D01

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Co-author(s):

Generation of Microenvironmentally Attuned Endothelial Cells by SOX7 and ERG Transcription Factors Preserves Embryonic Patterning

Endothelial cells (ECs) constitute the fundamental building blocks of all vascular networks, yet current in vitro models fail to capture the molecular and functional heterogeneity that defines organ-specific vasculature. This work demonstrates the novel finding that synergistic induction of SOX7 and ERG in hPSC-derived barrier forming cells of a neuroectodermal lineage (iBFCs) can successfully convert them into phenotypically marked reprogrammed ECs (SE-rECs). These cells are transcriptomically and proteomically congruent to adult ECs from various human vascular beds while retaining aspects of brain-specific HOX gene patterning and microenvironmentally attunement. Additionally, SE-rECs functionally recapitulated core endothelial programs including angiogenic morphogenesis and inflammatory activation. When co-cultured with human astrocytes and pericytes, SE-rECs upregulated BBB-associated genes (CLDN5, MFSD2A, SLC2A1) and acquired enhanced barrier characteristics absent in generic ECs in vitro. Integration of SE-rECs into a three-dimensional microfluidic BBB-on-chip model under flow further reinforced BBB-specific phenotypes, including decreased permeability and activation of WNT/Î²-catenin and shear-responsive pathways. Altogether, SE-rECs have been shown to be a robust platform for modeling the BBB, investigating neurovascular development and pathology, and advancing the discovery of targeted therapeutics capable of traversing into the brain. This dissertation demonstrates that adoption of organotypic endothelial phenotypes requires both appropriate transcriptional circuitry and embryonically aligned spatial patterning establishing a principle that can be used to develop future reprogramming strategies.

D02

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Extended synaptotagmins: Key regulators of plasma membrane integrity and lung remodeling

Rationale: Extended synaptotagmins (ESyts) are endoplasmic reticulum-plasma membrane tethering proteins that play key roles in lipid transfer and plasma membrane repair. Although their functions are described in cellular membrane homeostasis, role in lung physiology and response to chronic cigarette smoke exposure remains poorly understood. Here, ESyt family proteins deficiency was investigated to determine their role in lung plasma membrane integrity and extracellular matrix homeostasis using a cigarette smoke exposure model. Methods: Male and female C57BL/6J and ESyt1-3 triple knockout mice were exposed to cigarette smoke five times per week for nine months. Pulmonary function was assessed through forced oscillation and expiratory measurements. Masson's trichrome staining was used to evaluate collagen deposition in the lung tissue sections, and airspace enlargement was quantified by mean linear intercept analysis using ImageJ (Fiji) software. RNA sequencing was performed on A549 cells stably expressing scrambled or ESyt2 shRNA to identify ESyt2-dependent molecular pathways. Results: Pulmonary function assessments revealed decreased forced expiratory volume (FEVâ,€.â,,), and compliance in ESyt1-3 triple KO mice. Additionally, the FEVâ,€.â,,/FVC ratio was reduced in cigarette smoke-exposed ESyt1-3 triple KO mice. Masson's trichrome staining revealed increased collagen deposition in the lungs of cigarette smoke-exposed ESyt1-3 triple KO mice compared to room air-exposed wild-type and triple KO mice. Mean linear intercept measurements showed enlarged airspaces in ESyt1-3 triple KO mice under both room-air and smoke exposure. RNA sequencing identified 804 differentially expressed genes in cells expressing ESyt2 shRNA. Discussion:Loss of ESyt1-3 function leads to reduced lung compliance, restrictive physiology, and enhanced collagen deposition and airspace enlargement. At the cellular level, ESyt2 depletion alters signaling pathways related to ECM organization.

D03

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Dual Lineage Tracing Identifies Cellular Mechanisms Underlying Radiation-Associated Changes in Atherosclerotic Lesion Composition

Background: Phenotypic plasticity of smooth muscle cells (SMs) and endothelial cells (ECs) influences atherosclerotic plaque composition and stability, but how changes in one population affect the other under vascular stress, such as irradiation, remains unclear. A major limitation has been the inability to simultaneously fate-map both lineages within the same lesion.
Methods: We generated dual lineage-tracing Apoe/ mice to simultaneously track SMC- and EC-derived cells. Mice underwent irradiation and bone marrow transplantation followed by Western diet-induced atherosclerosis. Lesions were analyzed using lineage tracing, immunostaining, and single-cell RNA sequencing (scRNA-seq). Histological analysis included Picrosirius Red staining for collagen organization, Modified Russell-MOVAT staining for lesion composition, and Ter-119 immunostaining to detect intraplaque hemorrhage.
Results: Dual lineage tracing enabled specific identification of SMC- and EC-derived cells in healthy and diseased vessels. Irradiation produced divergent responses: SMC-derived cells showed reduced lesion investment and increased inflammatory gene expression, while EC-derived cells expanded and expressed SMC-associated genes. However, EC-derived cells failed to induce extracellular matrix programs, and irradiated lesions exhibited reduced collagen content and decreased ACTA2+ fibrous cap cellularity, indicating reduced plaque stability.
Conclusions: Dual lineage tracing confirms that irradiation-induced loss of lesional SMCs and expansion of EC-derived ACTA2+ cells reflect true shifts in cellular dynamics rather than lineage misclassification. These findings reveal coordinated SMC and EC reprogramming, impaired extracellular matrix organization, and reduced fibrous cap stability that may contribute to increased atherosclerotic cardiovascular disease risk following radiation exposure.

D04

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Total Sphingomyelin Synthesis Deficiency Promotes Lipodystrophy and Prevents Adipogenesis

Abstract

Lipodystrophy is a severe metabolic disorder marked by loss of adipose tissue, insulin resistance, fatty liver, and dyslipidemia. Disruption of serine palmitoyltransferase (SPT), the rate-limiting enzyme in sphingolipid synthesis, has been shown to trigger lipodystrophy, suggesting that downstream sphingolipid pathways may play critical roles in adipose homeostasis. Sphingomyelin synthases, SMS1 and SMS2, convert ceramide to sphingomyelin (SM) and thereby regulate the balance between these bioactive lipids. However, their role in adipose tissue integrity remains unclear.

In this study, we generated inducible Sms1 knockout (iSms1 KO) mice and combined iSms1 KO with germline Sms2 deficiency to achieve total SMS loss (dKO). SMS deficiency produced robust SM depletion and glucosylceramide accumulation in adipose tissue. Unexpectedly, ceramide levels were not significantly elevated. While iSms1 KO mice maintained normal adiposity under chow diet, likely due to existence of SMS2 activity, combined SMS1/SMS2 deficiency resulted in rapid and profound lipodystrophy. Adipocytes from dKO mice exhibited extensive apoptosis accompanied by marked macrophage infiltration. Remarkably, SM supplementation substantially rescued the apoptosis phenotype. Mechanistically, total SMS deficiency markedly increased caveolin-1 and PTEN(phosphatase and Tensin homolog) levels and suppressed activated -AKT, revealing a previously unrecognized SM-caveolin-1-AKT survival axis in adipocytes. In parallel, studies in stromal vascular fraction-derived adipocytes demonstrated that loss of SMS activity impairs adipogenesis, in part through induction of membrane-bound cadherins, known inhibitors of adipocyte differentiation.

In conclusion, total SMS activity-mediated SM but not ceramide changes in adipose tissues contributes to the adipocyte integrity and adipogenesis. Fine-tuning SMS activity could provide a new approach for the treatment of metabolic diseases.

D05

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Investigating Mucosal Immunity with Dual-glycoprotein VSV-based Vaccines

Human Immunodeficiency Virus (HIV) remains a significant global health challenge. According to the World Health Organization, in 2024, approximately 40.8 million people were living with HIV. HIV weakens the immune system's ability to defend against infections and diseases by destroying the body's cells such as CD4+ T cells, macrophages, and dendritic cells. We aim to develop a vaccine that functions at the later stage of a germline-targeting series, delivering protection directly to mucosal sites which are the main portals of entry for HIV.

We will be using the Vesicular Stomatitis Indiana Virus (VSV) as a vaccine vector. The VSV platform is highly immunogenic and adaptable, allowing for the expression of diverse antigens by replacing its glycoprotein with those from other pathogens. Our research focuses on developing dual-glycoprotein VSV vectors that express a stabilized HIV envelope glycoprotein (Env) alongside a functional glycoprotein to facilitate viral infection. We are evaluating several candidates, incorporating glycoproteins from Lassa virus (LASV GPC), SARS-CoV-2 (SCV2 Spike), and Marburg virus (MARV GP). These vectors were selected not only because they have been or are near evaluation in human clinical trials, but also for their ability to facilitate mucosal infection. Our studies include constructs combining LASV GPC, SCV2 Spike, and MARV GP, alongside expressing Env with or without a transmembrane domain, cytoplasmic region, and signal peptide derived from native VSV G (EnvG). Using the Mesocricetus auratus (Golden hamster) model, this project aims to identify the most effective vector candidates capable of eliciting strong mucosal immune responses and protective immunity. We have narrowed down the candidates to dual-glycoprotein constructs that contain MARV GP as the functional protein as they elicit a consistent strong mucosal and immune response. This research will advance the development of novel vaccines against mucosally transmitted pathogens.

D06

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Characterization of retinoid action in alveolar type 2 cells

Retinoids comprise a class of molecules, including vitamin A, whose primary function is transcriptional regulation. In the lungs, retinoids play a well-known part in development, though there is also evidence of their participation in adult lung physiology. Studies have unsuccessfully targeted retinoids in the search for therapeutic options for lung diseases, and the mechanism of retinoid action in the lungs remains poorly understood. Alveolar type 2 cells (AT2Cs) produce and secrete pulmonary surfactant, a fluid composed primarily of lipids that maintains alveolar patency, and whose dysregulation is implicated in several pulmonary disease states. Here, we examine the role that retinoids play in AT2Cs. Using A549 cells in culture at air-liquid interface, we model an AT2C-like phenotype in vitro. To broadly characterize potentially retinoid-responsive pathways, we performed a tyrosine phosphorylation (p-Tyr) screen in these AT2C-like cells treated with retinol or vehicle. Proteins that showed notable p-Tyr changes were CaSR (calcium-sensing receptor), GBE1 (glycogen branching enzyme), cytokeratin 8, and IL-1RA (interleukin-1 receptor antagonist), illustrating heterogeneity of responsive pathways. To examine retinoid delivery to AT2Cs, we developed an AT2C-like and fibroblast co-culture system which showed that AT2Cs respond transcriptionally to retinol-loaded fibroblasts as well as to retinol in media. Additionally, co-culture with retinol-loaded fibroblasts increases expression of ABCA3, a marker of AT2C differentiation. Future directions will aim to further characterize the role of retinoids in AT2C lipid metabolism, elucidate the mechanism of retinoid delivery to AT2Cs, and examine the effect of retinoid action on pulmonary function in vivo in health and diseased conditions. Additionally, characterizing the role of retinoids in AT2Cs could provide insight into potential therapeutic strategies for lung diseases.

D07

Irina Stavrovskaya Ph.D. Advisor(s): Itsaso Garcia-Arcos Ph.D.

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Acyl-carnitine profile alteration in primary alveolar type 2 cells in a bleomycin mouse model of pulmonary fibrosis

Pulmonary fibrosis (PF) is characterized by progressive destruction of alveolar architecture, epithelial injury, and excessive extracellular matrix deposition. Increasing evidence suggests that metabolic dysfunction in alveolar type 2 cells (AT2C) plays a leading role in disease initiation and progression. Among these metabolic alterations, impaired mitochondrial fatty acid oxidation (FAO) might stand as key driver of AT2C dysfunction. Acylcarnitines (ACs), essential intermediates in mitochondrial fatty acid transport and oxidation, serve as critical regulators of cellular energy homeostasis and lipid metabolism. However, their role in AT2C biology and specifically in PF is poorly understood.

Here, we investigated AC levels in primary AT2C isolated from mice challenged with bleomycin. Using targeted lipidomics profiling, we showed that PF is associated with pronounced alterations in multiple AC species in AT2C. Specifically, we observed a significant elevation of long-chain ACs (C14:0, C16:0, C16:1, C18:1) indicating impaired FAO. Most of the short-chain ACs (C2:0, C3:0, C4:0, C4-OH, C5-OH, C3:1-2OH, C4:1-2OH) were decreased, although not significantly, whereas very-long chain ACs (C22:1, C24:0, C24:1) showed a trend towards elevation.

Observed AC changes might result from defective carnitine uptake, deficiency of very-long chain acyl-CoA dehydrogenase (VLCAD) and long-chain L-3-hydroxyacyl-CoA dehydrogenase/trifunctional protein (LCHAD/TFP), as well as from deficiency in the mitochondrial carnitine shuttle system - carnitine palmitoyltransferase II/carnitine-acylcarnitine translocase (CPTII/CACT).

These findings provide new insight into metabolic mechanisms underlying AT2C dysfunction in a bleomycin model of PF and identifies ACs metabolism as a potential target for disease treatment.

D08

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Alveolar type II cell-specific LRP1 loss worsens pulmonary fibrosis and emphysema in mice

Pulmonary fibrosis (PF) is a chronic interstitial lung disease with poor prognosis, and minimal therapeutic options, characterized by excessive collagen deposition and progressive loss of lung compliance. Repeated alveolar surfactant-producing type II cells (AT2C) damage triggers fibrotic remodeling. Our studies revealed that mice with AT2C-specific deletion of low-density lipoprotein receptor-related protein-1 (SPC-LRP1â »/â ») exhibit reduced lung compliance and surfactants at baseline. We hypothesize LRP1 loss in AT2C predisposes the alveolar niche to fibrosis.
6-month-old wild-type (WT) and SPC-LRP1â »/â » male and female mice were challenged with repeated low-dose bleomycin (BLM), a well-established profibrotic drug, for 33 days of experimental period. Inflammation was monitored by body weight tracking, bronchoalveolar lavage (BAL) protein quantification and cellularity. Lung function was assessed whole body plethysmography and forced oscillatory techniques. Lung sections assessed for fibrosis (Ashcroft scoring) and emphysema (mean linear intercept quantification).
During BLM challenge, male WT mice showed compensatory faster breathing, while SPC-LRP1â »/â » males had slower breathing with prolonged airflow recovery after each breath. Female WT mice showed longer breathing pauses after inspiration, whereas SPC-LRP1â »/â » females had slower and shallower breathing. WBP data suggested impaired compensatory breathing patterns in SPC-LRP1â »/â » mice. Forced oscillatory techniques showed BLM challenge caused a restrictive pattern in WT mice, worsened in SPC-LRP1â »/â » males but not females. Histologically, male SPC-LRP1â »/â » mice showed severe fibrosis and increased chord length, indicating mixed fibrotic and emphysematous remodeling, while females showed severe fibrosis with reduced chord length, consistent with predominantly fibrosis. Higher BAL protein and cellularity indicated greater inflammation in SPC-LRP1â »/â » than WT, suggest AT2C-specific LRP1 loss exacerbates BLM-induced fibrosis

D09

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sevofluraine preconditioning has no effect on neuronal KIBRA levels in the CA1 hippocampal region of anesthetized adult male mice: implications for PKMÎ¶ protein stability

Kidney and Brain Expressed protein (KIBRA) is a postsynaptic scaffolding protein closely linked to memory, cognitive function, and synaptic plasticity (Porter et al., 2018). KIBRA stabilizes PKMÎ¶ and supports maintenance of long-term potentiation (LTP). A 2024 study demonstrated that PKMÎ¶-KIBRA coupling is required for sustaining long-term memory and LTP (Tsokas et al., 2024). However, the potential neuroprotective role of this complex during hypoxic or ischemic stress-conditions relevant to the operating room-remains unclear. Preconditioning hippocampal slices with the inhaled anesthetic sevoflurane increases PKMÎ¶ expression and has been proposed as a mechanism of neuroprotection (Wang et al., 2012). However, these findings are limited to in vitro models (Sacktor, 2011). We therefore evaluated whether sevoflurane increases PKMÎ¶ and KIBRA expression in vivo. Wild-type mice were exposed to either 4% sevoflurane in 100% oxygen or 100% oxygen without anesthesia. Brains were harvested, coronally sectioned, and stained with ALEXA647 and ALEXA488 to assess PKMÎ¶ and KIBRA expression. After 2 hours of 4% sevoflurane exposure in vivo, immunocytochemistry showed increased PKMÎ¶ expression in the CA1 pyramidal cell body layer, but not in the dendritic stratum radiatum. No increase in KIBRA was observed in any layer on CA1, suggesting that PKMÎ¶-KIBRA complex formation in dendrites is specific to LTP-related processes (Tsoaks et al., 2024). Thus, sevoflurane increases PKMÎ¶ expression without a concomitant rise in KIBRA. These findings suggest that KIBRA is not required for PKMÎ¶-mediated neuroprotection during anesthetic preconditioning, highlighting the differential regulation of PKMÎ¶ in neuroprotection versus memory encoding.

D10

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Sevoflurane preconditioning causes an increase in somatic but not dendritic PKMÎ¶ in the CA1 hippocampal region of anesthetized adult male mice: functional implications of PKMÎ¶ compartmentalization

Protein Kinase MÎ¶ (PKMÎ¶) is a constitutively active, brain-specific member of the atypical protein kinase C family that plays a key role in long-term potentiation (LTP) and long-term memory storage in the hippocampus. Its importance was demonstrated when intrahippocampal injection of the PKC inhibitor ZIP caused persistent memory loss in mice (Pastalkova et al., 2006). Beyond memory, PKMÎ¶ also has neuroprotective properties: increasing its levels in vitro reduces hypoxia-induced damage in pyramidal neurons. Notably, preconditioning hippocampal slices with the inhaled anesthetic sevoflurane increases PKMÎ¶ expression, serving as a mechanism in mediating neuroprotection against hypoxic/ischemic injury (Wang et al., 2012).

However, these findings have largely been limited to in vitro hippocampal slice models (Sacktor, 2011). Hypoxic and ischemic events are clinically relevant in the operating room, where excitotoxic injury can cause irreversible depolarization and neuronal death. Thus, it is important to evaluate whether sevoflurane increases PKMÎ¶ expression in vivo and whether this confers neuroprotection in intact hippocampal tissue. Additionally, because PKMÎ¶ is implicated in both memory formation and neuroprotection, it remains unclear how the brain distinguishes between these functional roles.

To address this, two groups of genetically identical mice were exposed in vivo to either 4% sevoflurane or oxygen. Brains were harvested, sectioned coronally, and stained with ALEXA647 to assess PKMÎ¶ expression in hippocampal regions. Immunocytochemistry revealed increased PKMÎ¶ expression in the CA1 pyramidal cell body layer of the hippocampus following 4% sevoflurane exposure without any changes in the corresponding dendritic layer (stratum radiatum). Comparisons with prior studies suggest region-specific and context-dependent PKMÎ¶ localization, which may help in explaining how the hippocampus differentiates its roles in memory consolidation versus neuroprotection.

D11

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AI-Guided Behavioral Phenotyping and Immunohistochemical Markers as Early Biomarkers of Post-traumatic Epilepsy

Following traumatic brain injury (TBI), a subset of individuals develop epilepsy; however, the biological mechanisms driving this transition remain poorly understood. The hippocampus has been extensively implicated in the pathogenesis of post-traumatic epilepsy (PTE) and associated cognitive impairment. Animal models of mesial temporal lobe epilepsy (mTLE) have revealed pronounced structural and functional alterations within hippocampal circuiry. Recent studies further indicate that altered pose dynamics detected using AI-guided behavioral phenotyping (MoSeq) during epileptogenesis can predict the occurrence of spontaneous seizures in mouse models of mTLE. The extent to which MoSeq-derived behavioral signatures predict seizure susceptibility following TBI, and whether such behavioral alterations correspond to immunohistochemical (IHC) remodeling within hippocampal networks, remains unresolved.

To address this, we combined MoSeq with hippocampal immunohistochemistry to identify candidate biomarkers associated with epileptogenic changes following experimental TBI. Adult mice were subjected to controlled cortical impact (CCI; n = 4) or sham surgery (n = 2) and, four weeks later, underwent open field and novel object place testing to assess general locomotion and spatial memory, respectively. Following behavioral assessment, hippocampal tissue was processed for immunostaining to evaluate dentate granule cell organization (Prox1), astrocyte and microglial reactivity (GFAP, IBA1), synaptic remodeling (ZnT3, Gephyrin), chronic granule cell activation (Î”FosB), and plasticity-associated signaling (KIBRA). We hypothesize that a subset of CCI animals will exhibit behavioral alterations accompanied by changes in expression patterns of IHC markers within the dentate gyrus. Future studies will determine whether these candidate biomarkers can serve as predictors of seizure outcomes following experimental TBI.

D12

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Predictive Physiological Biomarkers of Post-Traumatic Epilepsy

Post-traumatic epilepsy (PTE) is a chronic, difficult to treat epilepsy subtype that develops after a traumatic brain injury (TBI). Despite decades of research, clinicians can not reliably predict PTE development in TBI patients. This study addresses this critical unmet need by uncovering robust, predictive physiological biomarkers of PTE. We conduct intracranial electroencephalography (EEG) recordings in a rodent model of TBI. This model uses the controlled cortical impact (CCI) procedure to induce a severe cortical injury, which leads to epileptiform activity and seizures in up to 40% of rats. Video-EEG recordings are then conducted over 24-hour periods in the acute (days 0-14) and chronic (days 15-200) phases. The acute period is designed to reflect recordings done in a hospital setting after a TBI. These early recordings are assessed for biomarkers including electrical and sleep patterns. Chronic recordings are used to evaluate PTE status by tracking the development of chronic spontaneous recurrent seizures. This work utilizes spectrograms, semi-automatous seizure detection pipelines, machine learning feature selection systems, and deep neural networks. Future directions will involve evaluating the predictive capacity of these biomarkers. Additionally, this preclinical pipeline will be used to evaluate the efficacy of therapeutic interventions including prophylactic use of brivaracetam, a synaptic vesicle glycoprotein 2A ligand anti-seizure medication.

D13

Rana Azab B.S. Advisor(s): Salvador Dura-Bernal Ph.D.

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Astrocytic calcium dynamics under neuromodulator drive:an integrated imaging-modeling framework with implications for ALS

Astrocytes are central regulators of excitatory neurotransmission, particularly in the cortex, where they couple intracellular calcium signaling to the release and uptake of glutamate. Astrocytes not only modulate glutamate clearance through high affinity transporters localized to the membrane, i.e., glutamate transporter 1 (GLT-1/EAAT2), they also enable calcium dependent vesicular and non-vesicular glutamate release. As a result, astrocytes critically shape neural circuit dynamics, specifically synaptic plasticity, excitatory tone, and network homeostasis. In healthy brain states, astrocyte mediated uptake effectively regulates glutamate transients through spatiotemporal precision. However, pathophysiological states, i.e., amyotrophic lateral sclerosis (ALS), demonstrate impaired astrocytic calcium signaling, fostering excitotoxic cascades and progressive motor neuron degeneration. Whether distinct calcium signaling motifs can “encode” neuromodulator identity, and how such “encoding” may be mapped onto the glutamatergic output under pathophysiological context remains unknown, a gap that obscures potential avenues for exploring neural circuit and synaptic adaptability in motor neuron diseases. To address this, we analyzed astrocytic calcium dynamics during in vitro neuromodulator application across amplitude, temporal kinetics, and spatial synchrony. The experimentally derived population level signatures provided empirical parameters to calibrate our in-silico model, which successfully simulated the intracellular pathways coupled to calcium dependent glutamate release and extracellular diffusion of relevant molecules, effectively reproducing the experimentally observed calcium waveforms. Our multimodal framework characterizes the mechanisms through which astrocytic calcium dynamics govern excitatory signaling and has potential to identify preliminary targets in neuron-glial networks for therapeutic interventions.

D14

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

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Identifying cell-type-specific alterations underlying schizophrenia-related deficits in auditory steady-state response: insights from a multiscale model of auditory thalamocortical circuits

Schizophrenia (Scz) impacts millions of individuals in the United States, posing significant challenges to healthcare systems and society due to its complex symptoms and the limited effectiveness of current treatments. While existing therapies primarily target positive symptoms, such as hallucinations, they often fail to address the negative and cognitive symptoms that severely impair quality of life. Furthermore, a substantial proportion of patients show resistance to these treatments. To address these unmet needs, this project seeks to deepen our understanding of Scz by focusing on an electrophysiological biomarker of sensory processing deficits: reduced 40Hz Auditory Steady-State Response (ASSR). Using a biophysically detailed computational model of the auditory thalamocortical circuit, we will integrate multimodal data-including electrophysiology, imaging, and transcriptomics-to capture the dynamics of healthy auditory processing at multiple levels, from individual neurons to macroscopic electro/magnetoencephalography (EEG/MEG) signals. This model will then be adapted to incorporate Scz-specific data, enabling simulations that reveal how cellular and circuit-level disruptions contribute to biomarker abnormalities. By focusing on these biomarkers, the project avoids the challenges of directly modeling complex symptoms, instead targeting the underlying neurobiological mechanisms. The refined model will serve as a platform to explore novel therapeutic interventions, focusing on pathways implicated in Scz, including glutamatergic, GABAergic, and neuromodulatory systems. This work aims to bridge the gap between basic neuroscience and clinical application, identifying mechanism-based treatments that could improve outcomes for individuals with Scz.

D15

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Functional and Cytoarchitectural Characterization of a hiPSC-Derived Midbrain Organoid Model of Sporadic Tauopathy

Background: Progressive supranuclear palsy (PSP) is a primary, sporadic tauopathy characterized by abnormal tau accumulation in neurons and glia. Human induced pluripotent stem cell (hiPSC)-derived organoids are powerful tools to model patient-specific genetic contributions and capture early changes preceding pathology. Molecular mechanisms that drive PSP pathology remain unknown, and organoids represent a clinically relevant model system to discover and validate candidate disease mechanisms.
Methods: Midbrain organoids from sporadic PSP patient (n=7) and matched control (n=5) hiPSC lines were generated and cultured for 10 months. For calcium imaging, organoids were incubated with 10uM Fluo-4-AM and imaged in media using a spinning disk confocal microscope. FIJI was used for manual ROI extraction and a custom code was used for analysis and event detection. For tissue clearing, organoids were delipidated with aqueous detergents, immunolabeled for cell-type specific markers and cleared with ACB buffer. Imaging was performed using confocal microscopy, and Imaris 10.2 was used for 3D analysis.
Results: Confocal imaging revealed robust Fluo-4-AM signal in all organoids, with activity consistent with neuronal calcium transients. Neurons had a diversity of firing patterns and rates, including tonic and bursting cells. The average firing rate trended higher in control organoids ($p=0.049$), and this effect was stronger in the 90th percentile of active cells ($p=0.033$). Tissue clearing revealed large TH- and MAP2-positive neurons with complex, long-range branching.
Conclusion: We demonstrate that midbrain organoids are physiologically active at 10 months with a diverse and morphologically complex neuronal population, with functional differences between PSP and control organoids. Ongoing studies will interrogate network-level activity and 3D neuronal morphology to reveal early changes associated with sporadic disease, ultimately informing therapeutic development.

D16

Hannah Johnson MPH Advisor(s): Thomas Deuel M.D.

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Diffusion Tensor Imaging Analysis of a Patient Diagnosed with Dementia

Over 6.7 million Americans live with Alzheimer's Dementia, the most common form of dementia. Dementia staging is crucial for determining treatment, level of care, and assisting families; this is performed with the Clinical Dementia Rating (CDR) Scale. This study seeks a more objectively quantitative alternative to the CDR Scale, which might replace or supplement the CDR as a means to stage dementia.

The CDR Scale has been the gold standard for staging dementia since 1982. The scale prompts caregivers with subjective questioning and assigns a point value to deficits in patients' memory, orientation, judgment, community affairs, home/hobbies, and personal care. A score of 0.5 is very mild dementia, 1 mild, 2 moderate, and 3 severe. Cholinesterase inhibitors are recommended for mild disease and memantine for moderate to severe. This study explores an alternative method for staging dementia by comparing DTI metrics in key white matter tracts between one patient with dementia to a dataset of 149 control patients without dementia.

Cognitive status was assessed at baseline using the Clinical Dementia Rating Scale - Sum of Boxes. In addition, caregiver-reported changes in daily functioning and behavior were systematically documented. Following cognitive testing, the patient underwent diffusion tensor imaging. DSI studios was used to extract DTI metrics from the patient and from 149 healthy controls collected from the NIMH healthy volunteer dataset. The dementia patient's DTI was normalized to the healthy volunteer dataset, and age matched to accurately compare DTIs.

Results indicated that the parahippocampal white matter tracts were significantly impaired in the dementia patient compared to the controls. Existing literature corroborates that dementia involves the hippocampus and parahippocampus tracts, both of which are involved in memory.

These findings suggest that DTI metrics may provide a more definitive alternative or supplement to the CDR scale for dementia.

D17

Syamantak Mukherjee Advisor(s): Alexandro Ramirez Ph.D.

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Characterizing Neural Correlates of internally-generated Eye Movements in Larval Zebrafish

The vertebrate visuomotor system enables animals to orient their gaze and movements in response to salient stimuli. One of the key components of this system is the optic tectum (superior colliculus in mammals), a midbrain structure that integrates spatially organized visual input with other sensory modalities to guide orienting and evasive behaviors. While the tectum's stimulus-driven responses are well characterized, it remains relatively unresolved whether the same circuits also contribute to spontaneous or internally-generated eye movements in the absence of visual input. Previous work has shown that spontaneous saccade timing in the larval zebrafish depends on hindbrain neurons exhibiting ramp-to-threshold dynamics. However, a clear role for the tectum and its dynamics in the absence of visual stimulus is yet to be determined. To address this, we investigate horizontal eye movements in larval zebrafish (Danio rerio) without visual stimulus. Larval zebrafish are an ideal model due to the conservation of tectal architecture with premotor connections and the accessibility of whole-brain imaging in transparent larvae. Larvae were immobilized in agarose dorsal side up, with space around eyes to facilitate movement and two-photon calcium imaging was used to monitor population-level and single-neuron activity across the brain during spontaneous behavior. 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. Preliminary findings show that no neurons in the tectum are positively correlated with spontaneous horizontal saccades, suggesting that the tectum may not play a role in eye movements in absence of visual stimulus. In addition, we observed activity in the forebrain, pointing to the possibility of an alternative circuit for eye movement control. These findings can potentially expand our understanding of the networks involved in internally-generated behaviors

D18

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

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Impact of Dendritic Morphology and Channel Conductances on NMDA Plateau Potentials in MSNs

Striatal medium spiny neurons (MSNs) generate NMDA receptor-mediated dendritic plateau potentials essential for basal ganglia computation. In Huntington's disease (HD), progressive dendritic atrophy precedes neuronal death, but whether structural loss or altered channel properties drives impaired plateau generation remains unresolved - a distinction with direct therapeutic implications. Compartmental NEURON simulations were run on D1 (n=10) and D2 (n=10) WT MSN reconstructions from the Luebke lab (Kotaleski 2023 model; identical conductance set on both subtypes). Clustered glutamate input was delivered at medial dendritic sites. Plateau detection required sustained depolarization above -40 mV for at least 50 ms, excluding action potentials. Morphological predictors were regressed against plateau properties and a pilot channel sweep varied gKir and gCaL. D1 MSNs generated robust plateaus (85.7% rate; amplitude 45.5+/-7.4 mV). D2 MSNs produced only brief transients (0.1-0.2 ms) that reached similar peak voltages but did not sustain above threshold for 50 ms and were classified as spikes, not plateaus. This difference (D1 85.7% vs D2 0%; Fisher's exact $p<0.001$; Cohen's $h=2.8$) arose under identical channels. D1 cells had greater dendritic length (+18.7%) and branch point density (+22.3%), and dendritic extent correlated negatively with response transience ($r=-0.49$, $p=0.038$), implicating geometry in sustaining the regenerative NMDA current. These results indicate that dendritic morphology is the primary determinant of plateau capacity under wild-type channel conditions. A pilot channel sweep (gKir and gCaL each at 0.5Ã—, 1.5Ã—, 2.0Ã—) confirmed D1 duration is robust to channel variation (7.18-7.36 ms), while no tested combination restored a plateau in D2 cells (all <0.20 ms). Morphology sets a ceiling that channel modulation cannot overcome in the range tested. Whether larger perturbations can cross that ceiling in HD-atrophied D1 cells is the critical next step.

D19

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Co-author(s):

Learning to Learn: How Cognitive Control Training Improves Learning

Prior experience shapes how organisms learn in novel situations. However, most learning and memory animal research studies use naÃ¯ve 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 were required 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 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 memory tasks that have unrelated cognitive or sensory features of APA.
We first assessed recognition memory using object-context, object-place, and object-location tasks. Mice demonstrated significant discrimination in two of three recognition conditions, with the third showing a trend toward significance, confirming reliable discrimination. We then administered cognitive control training (CCT) using the APA task, while control mice underwent the identical training experience without shock. Three days after training, recognition memory was reassessed using the same object-context, object-place, and object-location tasks. Data analysis of the post-training comparisons is ongoing.

D20

Catherine Solis Advisor(s): Stephen Macknik Ph.D.

Co-author(s): Susana Martinez-Conde, Robert Alexander, Stephen Waite, Shawn Lyo, Ashwin Venkatakrishnan, Arcadij Grigorian

Microsaccades help radiologists detect abnormalities in chest x-rays

Microsaccades improve visual processing in many domains, including visual search. However, no study to date has investigated the role of microsaccades while searching medical images for abnormalities. In radiology, failing to detect abnormalities is a substantial source of interpretive error with major consequences. Because interpretation of radiologic images is the first step of the diagnostic pathway, a missed abnormality can lead to termination of the diagnostic tree and patient morbidity and mortality. We conducted a psychophysical and eye-tracking study aimed at determining the gaze dynamics used by naive participants and trained radiologists as they searched for potentially cancerous abnormalities in medical images. Specifically, we conducted binocular gaze recordings while naive participants, radiology residents, and radiology attendings searched chest x-rays. Each x-ray image contained one abnormality (i.e. a nodule); participants were instructed to find that abnormality and to report its location. Irrespective of their expertise level, participants produced more microsaccades per fixation when looking at abnormalities than when looking at other parts of the images, showing that microsaccade production is heightened when radiologists look at critical image regions. These findings are consistent with the proposal that microsaccades help radiologists to accurately recognize abnormalities by enhancing information acquisition at key moments and image locations. Importantly, microsaccade production increased before participants correctly identified abnormalities, but not when they foveated abnormalities and then failed to report them. Our combined results suggest that microsaccades may be critical to the positive identification of abnormalities in medical searches.

D21

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

Co-author(s): -

Characterizing the Tg-MYOC mouse model and comparison with Tg-Cre-MYOC mice

Purpose: Glaucoma is a leading cause of blindness worldwide. The only modifiable risk factor is elevated intraocular pressure (IOP). Glaucoma therapies lower IOP to slow disease progression. Myocilin gene (MYOC) mutations are responsible for ~4% of primary open-angle glaucoma, the most common type in adults, and 10-40% of juvenile open-angle glaucoma. A transgenic mouse line (Tg-MYOC) carrying the pathogenic Y437H mutation in MYOC has previously been described to have early onset IOP elevation and cause functional deficits. We sought to further characterize a colony and evaluate its use as a glaucoma model. We also wanted to evaluate a recently acquired Cre inducible line (Tg-Cre-MYOC) with the same mutation.
Methods: Founders were obtained from Dr Zode at UCSD and maintained on a C57BL6 background. IOP was measured under inhaled isoflurane anesthesia with a rebound tonometer. PERG were performed using the JORVEC platform under ketamine/xylazine anesthesia. Cre expression was induced via microinjection of adenovirus containing Cre under the CMV promoter and GFP as reporter gene.
Results: The ages of mice ranged from 2 to 30 months. Mean IOP (Â±SD) was elevated in Tg-MYOC mice (16.0Â±5.7 mmHg) compared to WT littermates (12.4Â±4.3 mmHg). There was no significant difference in PERG amplitude, but there was increased mean latency in Tg-MYOC mice compared to WT littermates (105.4Â±22.4 vs 91.6Â±14.9 ms). In a small number of Tg-Cre-MYOC (N=3), IOP was elevated one week after injection compared to baseline (19.8Â±0.3 vs 15.2Â±0.6, $p<0.01$, paired t-test). Expression of mutant myocilin protein was confirmed by presence of dsRED reporter gene.
Conclusions: Although not as robust as reported in the original paper, the Tg-MYOC mice had elevated IOP and increased PERG latency suggestive of glaucomatous phenotype. The Tg-Cre-MYOC model may be better for future use, as the IOP elevation was more robust and there is less risk of loss of phenotype in future generations.

D22

Nicholas Stratigakis B.S. Advisor(s): John Danias Ph.D.,M.D.

Co-author(s):

Refinement of an Ex-Vivo Corneal Rim Perfusion Model

Purpose: We previously demonstrated the feasibility of a paired, bisected human corneal rim perfusion model to evaluate trabecular meshwork (TM) outflow. This study assessed the model's reproducibility across repeated trials and refined tissue preparation and mounting to improve physiologic accuracy and interface stability.
Methods: Human corneal rims obtained after penetrating keratoplasty were bisected and mounted to custom 3D-printed perfusion chamber devices using cyanoacrylate adhesive. Constant-pressure perfusion (8 mmHg) was maintained for ≥50 hours, followed by stepwise increases of 7.5 mmHg to 30 mmHg to assess pressure-flow linearity. Continuous pressure and flow were recorded. Repeated validation trials were analyzed to identify mechanical and methodological factors affecting performance, directly informing redesign of the tissue-device interface.
Results: Variability between paired halves and across trials demonstrated that model performance depended on mechanical and interface-related factors. Common findings included incomplete stabilization during the final stepwise validation phase and very low outflow facility. Likely contributors were adhesive migration toward the TM, irregular geometry of punched corneal rims creating angular sealing interfaces, variable adhesive volume, and micro-leak at non-uniform edges. Iterative testing clarified how tissue preparation and seal architecture influence physiological flow.
Conclusions: Findings guided redesign of the model but may present insurmountable problems when utilizing corneoscleral donor rims left over after corneal transplantation. Utilization of bisected anterior segments may be necessary to minimize adhesive proximity to the TM, increase sealing surface area, reduce angular stress points, and standardize tissue adaptation. Ongoing evaluation will determine whether this optimized approach enhances reproducibility for translational TM research.

D23

LeeAnn Marcello B.S. Advisor(s): Richard Kollmar Ph.D.

Co-author(s): Mark Stewart MD, PhD, Ofer Azoulay, MD

Functional Electrical Stimulation Following Hypoglossal-Facial Nerve Transfer: Development of a Preclinical Model for Enhanced Facial Reanimation

Unilateral facial paralysis is a distressing condition that can lead to blindness. In about one-third of cases it requires surgical intervention. Nerve transfer is the treatment of choice, but restoration of coordinated movement is unpredictable. We are developing a rodent model of hypoglossal-facial nerve transfer followed by functional electrical stimulation. We incorporate longitudinal, noninvasive monitoring of whisking during recovery to assess functional outcomes in a clinically translatable manner. Unlike the traditional reliance on histology in animal studies, we emphasize noninvasive assessment of reinnervation and motor recovery.

An end-to-side anastomosis was performed in which the hypoglossal nerve was partially incised and the severed facial nerve stump was sutured to it. Whisking was recorded with high speed videography in a custom-built illuminated enclosure in freely roaming, unanesthetized rats. Whisker motion will be quantified through video analysis using DeepLabCut, a markerless pose estimation based on transfer learning with deep neural networks.

Hypoglossal facial nerve transfer was performed so far in 15 Sprague Dawley rats and well tolerated. Intraoperative confirmation of each nerve was achieved by electrical stimulation with observed whisking and tongue movement. Whisking was recorded preoperatively to establish baseline function and postoperatively on days 7 and 14 and at months 1, 2, 3, and 4. As expected, whisker movement was absent on the experimental side following surgery. Verification of reinnervation through functional electrical stimulation at 4 months post-operation is pending.

Surgeries were completed in less than an hour, and each whisking assessment required about one minute to record. The surgical technique was standardized and reproducible, improving upon a previous pilot study. This provides a time and cost efficient approach compared with prior studies that relied on expensive and technically complex apparatuses.

D24

Amanda Azmi M.S.,B.S. Advisor(s): Thomas Wallach M.D.

Co-author(s):

Atopy Therapies and their Functionality in Alleviating Complications of Inflammatory Bowel Disease

Atopy is a predisposition to heightened immune responses to environmental antigens, commonly presenting in childhood as allergic rhinitis, eczema, or atopic dermatitis. Type 2 immune pathways are also involved in tissue repair after injury. Dupilumab, an IL-4/IL-13 inhibitor, has been shown to promote remodeling and reduce fibrosis in conditions such as eczema and eosinophilic esophagitis. Many complications of inflammatory bowel disease (IBD), particularly Crohn's disease (CD), are driven by abnormal fibrotic pathways. Small bowel obstruction (SBO) is a frequent IBD complication managed with gastric decompression or surgery. Prior work demonstrated lower rates of SBO and fistula formation in CD patients receiving Dupilumab. We aimed to assess whether Dupilumab use is associated with reduced SBO severity by evaluating risk of nasogastric (NG) tube decompression using TriNetX.
Methods:
A TriNetX comparative study assessed hazard risk of gastric tube decompression in patients with intestinal obstruction receiving Dupilumab versus not receiving Dupilumab. Patients with dermatitis/eczema and asthma were included, allowing overlapping atopic disease. Cohorts were propensity score-matched for age, sex, and race/ethnicity, with Kaplan-Meier analysis used to estimate hazard ratios; patients with prior outcomes were excluded.
Results:
Among 1,031 matched patients, 948 with obstruction were in the Dupilumab cohort and 959 in the non-Dupilumab cohort. Twelve patients in the Dupilumab group required gastric tube decompression versus 30 in the non-Dupilumab group. The hazard ratio was 0.478 (95% CI 0.243-0.944).
Conclusion:
Dupilumab use was associated with lower severity of SBO in IBD cohorts, consistent with prior findings. IL-4/IL-13 inhibition may reduce fibrotic formation or promote reparative remodeling. Increased event-free survival in Dupilumab-treated patients with prior SBO suggests attenuation of disease severity. Further research is warranted.

D25

Kianna von Maydell Advisor(s): Rena Orman Ph.D.

Co-author(s): Dr. Mark Stewart, M.D., Ph.D., Dr. Richard Kollmar, Ph.D.

Using Automated Cell Segmentation and Deep Learning Models for Quantification of Age-Dependent Cell Loss in Bat Brains

Bats are a powerful animal model for studying age-related changes in the brain due to their neuroanatomical similarities to humans, and their long lifespan (>15 years in captivity). Our previous imaging data shows that our captive population of fruit bats, Carollia perspicillata, exhibit age-dependent inhibitory cell loss in key brain regions like the hippocampus and claustrum. Accurate quantification of cell populations across brain regions is essential for understanding these changes, yet traditional segmentation methods struggle with densely packed nuclei and variable signal intensity. To address this, we adapted a fluorescence microscopy image analysis workflow that combines immunohistochemistry with deep-learning-based segmentation to compare overall cellular loss to inhibitory neuron loss in young and aged bat brains.

Three pairs of young (<4 y.o.) v.s. old (>7 y.o.) bat brains were fixed with PFA and sectioned. Sections were immunolabeled with parvalbumin (an inhibitory cell marker), latexin (a claustrum-specific marker) and the nuclear stain DAPI. 10X whole-section images were acquired and imported into QuPath, where the regions of interest were manually delineated. Inhibitory neurons within these regions were detected using channel-specific intensity and morphology classifiers, and detections were checked manually by trained individuals. To quantify the proportion of inhibitory cells lost in these brain regions, we applied the deep learning-based StarDist algorithm within QuPath for automated nucleus detection of the DAPI channel. StarDist models nuclei as star-convex shapes and uses a convolutional neural network trained to segment nuclei even in crowded fields, outperforming traditional segmenting approaches for dense and heterogeneous images.

We extracted counts of all nuclei and compared these to inhibitory cell counts across regions and age groups. Our analyses showed significant losses in the hippocampus and claustrum between young and old bats.

D26

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

Co-author(s):

An endogenous protein phosphatase 2A inhibitor contributes to fibrotic signaling in lungÂ fibroblasts

The activity of protein phosphatase 2A (PP2A), a serine-threonine phosphatase, is reduced in lung fibroblasts from patients with idiopathic pulmonary fibrosis (IPF). Chemical reactivation of PP2A reduces bleomycin-induced fibrosis in mouse models. However, the mechanism underlying reduced PP2A activity in IPF is unknown.

The objective of this study was to determine whether the endogenous PP2A inhibitor, cancerous inhibitor of PP2A (CIP2A), suppresses PP2A activity and enhances fibrotic signaling in lung fibroblasts.

CIP2A was overexpressed in primary lung fibroblasts using lentiviral technology. RNA sequencing evaluated gene expression changes following CIP2A overexpression. Several targets identified by RNA sequencing were validated by PCR and Western blotting. Fibroblasts were treated with inhibitors of Akt, ERK, and SMAD3.

Immunoprecipitation of PP2A from fibroblasts isolated from healthy and IPF subjects suggested increased PP2A-CIP2A binding in IPF samples. Silencing CIP2A enhanced PP2A responses in IPF fibroblasts. Transcriptome analysis of fibroblasts overexpressing CIP2A identified ~600 differentially expressed genes. Gene Ontology analysis revealed multiple pathways altered by CIP2A overexpression, including inflammatory responses, cell adhesion, regulation of cell migration, and extracellular matrix remodeling. Confirmatory analysis showed that CIP2A overexpression significantly upregulated fibrotic markers COL1A1 and CTHRC1 and inflammatory mediators IL1B, IL8, and CCL27. CIP2A overexpression also inhibited PP2A activity and enhanced phosphorylation of ERK, Akt, and SMAD3. Chemical inhibition of SMAD3, Akt, and ERK markedly reduced CIP2A-driven COL1A1 and CTHRC1 expression.

This study indicates that CIP2A negatively regulates PP2A activity in lung fibroblasts while modulating inflammatory responses, cell adhesion, cell migration, and extracellular matrix remodeling.

D27

Sonal Dharani M.S. Advisor(s): Richard Kolesnick M.D.

Co-author(s): Dr. Peter Bergold

CD28 Co-Stimulation Drives Ceramide-Rich Platform Assembly Required for T Cell Activation

Effective T cell activation requires coordinated signaling downstream of TCR/CD3 engagement and CD28 co-stimulation. Although CD28 is essential for full T cell activation, the membrane-proximal mechanisms that spatially organize its signaling remain incompletely defined. Ceramide-rich platforms (CRPs), generated by acid sphingomyelinase (ASMase), facilitate receptor clustering and signal amplification. We investigated whether CD28-mediated T cell activation depends on ASMase-driven CRP formation.

Jurkat T cells were stimulated with an agonistic CD28 antibody to characterize early signaling events. Phosphorylation of CD28 tyrosine residues Y191 and Y218 was assessed along with downstream PI3K and MAPK activation. CRP formation and CD28 membrane redistribution were analyzed by Immunofluorescence microscopy, and activation-associated gene expression was measured by RT-PCR. ASMase activity was inhibited pharmacologically using imipramine.

CD28 engagement induced phosphorylation of Y191 and Y218 within 45 seconds, preceding maximal PI3K and MAPK activation at 60-120 seconds. ASMase inhibition abrogated CRP formation eliminated phosphorylation of both tyrosine residues and markedly reduced downstream signaling. CD3 stimulation alone failed to induce CRPs, whereas CD3/CD28 co-stimulation triggered rapid CRP assembly and redistribution of CD28 from a diffuse membrane pattern into ceramide-enriched domains. ASMase inhibition prevented both CRP formation and CD28 relocalization. Functionally, CD3/CD28 co-stimulation significantly increased IL-2, PD-1, TNF-Î±, and IFN-Î³ expression, while imipramine suppressed these responses in a dose-dependent manner.

These findings shows that ASMase-driven ceramide-rich platform assembly is a critical upstream event in CD28 co-stimulatory signaling, required for phosphorylation of CD28 tyrosine residues and activation of PI3K/MAPK pathways, establishing membrane ceramide organization as an essential regulatory checkpoint in T cell activation.

D28

David Manrique M.S. Advisor(s): David Aggen Ph.D.,M.D.

Co-author(s):

Expanding Therapeutic Horizons: Durable Response to Novel Combination Immunotherapy with Enfortumab Vedotin and Pembrolizumab in Large Cell Neuroendocrine Urothelial Cancer

Approximately 90% of bladder cancers are urothelial carcinoma (UC), while other histological variants are far less common. Invasive UC often exhibits divergent differentiation resulting in multiple histologic variants, which are often aggressive, have poor clinical outcomes, and may require non-conventional approaches. Primary neuroendocrine tumors of the urinary tract account for <1% of all urothelial neoplasms. High grade large cell neuroendocrine carcinoma (LCNEC) is an aggressive tumor, associated with a dismal prognosis despite intensive treatment. Owing to its rarity, optimal management strategies are undefined, and treatment regimens are largely extrapolated from pulmonary LCNEC, commonly involving platinum-etoposide chemotherapy. Here, we describe the case of a platinum-ineligible patient with metastatic LNEC with an exceptional response to enfortumab vedotin (EV) and pembrolizumab. LCNEC remains a very rare subtype of bladder malignancy. Typically, metastatic UC patients are treated with standard of care cisplatin-based combination therapy, which have limited activity and are poorly tolerated. While combination EV and pembrolizumab in clinical trials has demonstrated objective response rates in clinical trials for metastatic UC, there has been little data on its effectiveness in LCNEC. To the best of our knowledge, this is the first report of a LCNEC tumor, with a substantial response after 3 cycles for at least 18 months and is ongoing. As demonstrated in previous publications and as we have also shown here, vedotin antibody-drug conjugates in combination with PD-1 inhibitors, such as pembrolizumab, can enhance antitumor activity to a greater extent than chemotherapy.

D29

Shayaan Satti Advisor(s): Chongmin Huan Ph.D.

Co-author(s):

Systemic Lupus Erythematosus: PCR Genotyping in 3H9 Mice

Systemic lupus erythematosus (SLE) is an autoimmune disease marked by the production of anti-dsDNA antibodies, which specifically target double-stranded DNA within the cell nucleus. The 3H9 gene is a knock-in immunoglobulin heavy chain gene used to study B cell development and self-reactivity. On their own, mice carrying the 3H9 gene are generally healthy and exhibit normal B cell development, as tolerance mechanisms effectively keep autoreactive cells in check. However, when the 3H9 heavy chain is paired with certain light chains, it can form B cell receptors that recognize DNA, making these mice a valuable model for studying autoreactive B cells and lupus-like disease. However, when 3H9 mice are crossed with other genetically modified strains, such as SMS2 knockout mice, tolerance mechanisms are disrupted, allowing for the survival and differentiation of 3H9 anti-dsDNA B cells. This 6-week study aimed to accurately genotype mice for the 3H9 gene using polymerase chain reaction (PCR). Genomic DNA was extracted from ear punch biopsies by heating in NaOH solution and then neutralizing with Tris-HCl buffer. PCR amplification was performed using 3H9-specific forward and reverse primers, along with a standard master mix containing buffer, dNTPs, MgClâ,,, and Taq polymerase. PCR products were analyzed by agarose gel electrophoresis at 110 V, stained with ethidium bromide, and visualized under UV light, with a distinct 450 bp band indicating the presence of the 3H9 gene. Positive controls (previous 3H9-positive DNA) and negative controls (double-distilled water) were included to validate the results. Out of six samples, two were identified as 3H9-positive. Flow cytometry data from previous work showed altered survival of autoreactive B cells in SMS2-deficient mice with the 3H9 gene, suggesting a role for SMS2 in B cell tolerance. The primary aim of this study is to explore the relationship between the 3H9 gene and SMS2 as a means to lay the foundation for future research.

D30

Julia Stolyar B.A. Advisor(s): Jared Jagdeo M.D.,M.S.

Co-author(s): Margaret Kabakova, BS, Paras Patel, DO, Julie Saadia-Hazkour, BS, Evan Austin, MD, PhD

Superior Induction of Apoptosis by Blue Light Compared to Red Light Photodynamic Therapy in Cutaneous Squamous Cell Carcinoma Keratinocytes

This study compares apoptosis induction in squamous cell carcinoma keratinocytes following exposure to 5-aminolevulinic acid combined with either blue light (417 Â± 5 nm) or red light (635 Â± 5 nm) photodynamic therapy, with apoptotic activity quantified via levels of Annexin V expression. Our results demonstrate that blue light induces superior levels of apoptosis in squamous cell carcinoma keratinocytes compared to red light at the parameters tested. Both wavelengths demonstrated additional dose- and temperature-dependent effects across two squamous cell carcinoma cell lines. These conclusions have significant implications for the clinical selection of a light source in combination with 5-aminolevulinic acid photodynamic therapy in the treatment of actinic keratosis and early squamous cell carcinoma lesions.

D31

Renata Sanders M.D. Advisor(s): Renata Sanders M.D.

Co-author(s):

Schizophrenia or Delirium? Psychosis-Dominant Delirium in the Setting of Sepsis and Multiorgan Failure - A Case Report

Delirium is a neuropsychiatric syndrome characterized by acute disturbances in attention, awareness, and cognition, frequently occurring in the context of severe medical illness. While perceptual disturbances may occur, delirium dominated by psychotic features-particularly vivid hallucinations and paranoid delusions-is rareÂ and can lead to diagnostic confusion with primary psychotic disorders.
We describe a 39-year-old woman with a history of provoked deep vein thrombosis (June 2025, Ghana; never anticoagulated) who presented in septic shock secondary to right lower extremity cellulitis. Her course was complicated by multiorgan failure, including acute kidney injury requiring dialysis, respiratory failure, and transient encephalopathy. After medical stabilization and surgical wound debridement, she developed acute onset florid psychosisÂ characterized by visual and auditory hallucinations of “spirits” and “dead people,” persecutory delusions regarding hospital staff, emotional lability, and marked disorganization. Neurologic evaluation and metabolic workup, including MRI brain and EEG, were unremarkable. Psychiatry diagnosed hallucinations of “spirits” and “dead people,” persecutory delusions regarding hospital staff, emotional lability, and marked disorganization. Neurologic evaluation and metabolic workup, including MRI brain and EEG, were unremarkable. Treatment with olanzapineÂ led to significant improvement in attention, organization, and affect regulation, with near-complete resolution of psychotic symptoms within one week.
This case illustrates an unusual psychotic presentation of deliriumÂ following septic shock and multiorgan dysfunction. The prominence of hallucinations and delusions initially obscured the underlying medical etiology, emphasizing the diagnostic challenge of distinguishing delirium from primary psychotic disorders in the medically ill.
Clinicians should consider delirium in the differential diagnosis of new-onset psychosis.

D32

Renata Sanders M.D. Advisor(s): Renata Sanders M.D.

Co-author(s):

Masked by Malignancy: Diagnostic Overshadowing of Anorexia Nervosa in Pediatric Leukemia

Eating disturbances are common in pediatric oncology; however, primary eating disorders may be obscured by medical illness, leading to delayed recognition and misattribution of psychopathology to treatment effects. As survival rates improve, psychiatric comorbidities in medically complex youth require careful diagnostic clarification.

Case Report:

X, a 14-year-old male with T-cell acute lymphoblastic leukemia in remission on maintenance chemotherapy, presented with severe weight loss and psychiatric distress during an oncology admission. Over one year, he lost 61 pounds despite medical stability. Weight loss was accompanied by excessive exercise, rigid restriction, body image distortion, and intrusive food-related obsessions. Psychiatric history included recent diagnoses of major depressive disorder and anorexia nervosa, with prior inpatient admission for suicidal ideation.

On evaluation, X demonstrated dysphoric affect, impaired insight, and significant food-related distress. A Yale-Brown Obsessive Compulsive Scale score of 29/40 indicated severe obsessive-compulsive symptoms. An Eating Attitudes Test (EAT-26) score of 59 further supported clinically significant eating-disorder pathology. While depressive symptoms were present, restrictive behaviors and obsessive food-related cognitions were identified as the primary drivers of impairment, distinguishing his presentation from cancer-related cachexia or treatment side effects.

Low-dose olanzapine (2.5 mg nightly) was initiated with mild improvement in meal-related anxiety. Despite recommendations for specialized inpatient eating-disorder treatment, placement was limited by ongoing oncologic care requirements, highlighting systemic barriers for medically complex adolescents.

Conclusion:

This case illustrates the risk of diagnostic overshadowing in pediatric oncology and underscores the importance of distinguishing treatment-related weight changes from primary eating-disorder psychopathology.

D33

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

Co-author(s):

Expanding Translational Transcriptomics at the Institute for Genomics in Health

Resolving cellular heterogeneity, spatial gene expression, and transcript isoform complexity is essential for understanding the molecular basis of complex disease, yet conventional bulk RNA sequencing approaches often obscure biologically critical variation. To address this, the Institute for Genomics in Health (IGH) at SUNY Downstate Health Sciences University has expanded its transcriptomics infrastructure in partnership with 10x Genomics Inc. to support multi-modal, high-resolution investigation across multiple disease areas. Using the 10x Chromium X platform, IGH offers single-cell and single-nucleus RNA sequencing (scRNA-seq/snRNA-seq), applied to profile cell-type-specific expression across human, mouse, and non-human primate samples spanning conditions including autism spectrum disorder (ASD), traumatic brain injury (TBI), and inflammatory bowel disease (IBD). Spatial transcriptomics via the 10x Genomics CytAssist Visium platform enables gene expression to be mapped onto intact tissue sections, preserving histologic context to characterize disease-specific molecular disruptions across neurological and gastrointestinal conditions. Long-read sequencing on the Oxford Nanopore PromethION supports full-length isoform profiling and detection of alternative splicing events in non-coding RNAs implicated in disease pathogenesis across these diverse sample types. Collectively, these platforms are actively generating high-dimensional transcriptomic datasets being analyzed to identify molecular signatures distinguishing disease from control states. These findings are expected to uncover novel gene regulatory networks and cell-type-specific pathways relevant to ASD, TBI, and IBD, advancing the translational mission of IGH as a shared genomics resource serving diverse investigators at SUNY Downstate.

D34

Lung Fu B.S. Advisor(s): Roseann Peterson Ph.D.

Co-author(s): Peter Barr

Atopic Dermatitis Is Associated with New Diagnosis of Depression: A Propensity-Matched Cohort Study Using the All of Us Database

Atopic dermatitis (AD) is a chronic skin disease characterized by eczematous lesions and pruritus. Prior studies show association with depression but lack temporal analysis.
Here, the aim was to determine if AD independently increases risk of incident depression and whether associations differ by demographics.
A retrospective propensity-matched cohort study using data from the All of Us Research Program (v8) was conducted. Adults with AD were matched to controls without AD based on age, sex, race, income, asthma, and allergic rhinitis. Patients with diagnosis of bipolar disorder or schizophrenia-spectrum disorders were excluded. Logistic regression was used to estimate the odds of having pre-existing depression at the time of AD diagnosis.
For longitudinal analyses, individuals with any history of depression prior to diagnosis of AD were excluded, and Cox proportional hazards models were used to estimate hazard ratios (HRs) for incident depression.
The matched cohort included 7,265 individuals with AD and 32,551 controls. Individuals with AD had twice the odds of pre-existing depression compared with matched controls (OR 1.97, 95% CI 1.85-2.09). AD was associated with a 2.25-fold increase in the odds of depression history in males and 1.84 in females.
In longitudinal analysis excluding prior depression, AD was associated with a 49% increased risk of developing new depression (HR 1.49, 95% CI 1.41-1.57, $p<0.001$). Risk was highest in the first year following AD diagnosis (HR 2.25) and remained elevated over 10-year follow-up (HR 1.73). Asian participants demonstrated higher risk (HR 2.22, 95% CI 1.54-3.20) of depression compared to White (HR 1.45), Black (HR 1.48), and Hispanic (HR 1.60) participants.
Atopic dermatitis is a predictor of subsequent depression, and Asian patients with AD may face a disproportionate risk of depression. These findings support depression screening for patients with AD, especially during the first post-diagnosis.

D35

Adrian Guin Rizzo M.S. Advisor(s): Roseann Peterson Ph.D.

Co-author(s): Tim B. Bigdeli, Peter B. Barr, Chris Chatzinakos, Markos Tesfaye, Gleda Kutrolli

A Meta-Analysis of Genome-Wide Association Studies of Depression in Latin American Cohorts: Interim Findings from the LAGC Major Depressive Disorder Working Group

Latin America and the Caribbean comprise more than 650 million individuals yet remain markedly underrepresented in psychiatric genetic research. Most genome-wide association studies (GWAS) of major depressive disorder (MDD) have focused on European ancestry populations, limiting generalizability and exacerbating global disparities in precision psychiatry. Latin American populations present additional analytic complexity due to recent genetic admixture and substantial heterogeneity in depression phenotyping.

The Latin American Genomics Consortium Major Depressive Disorder Working Group (LAGC-MDD) aggregated 33 datasets across Brazil, Colombia, Mexico, Peru, the United Kingdom, and the United States. Depression phenotypes were harmonized across cohorts using DSM-based diagnoses, ICD-coded electronic health records, structured interviews, and validated symptom scales. Cohort-level GWAS were conducted using ancestry-adjusted regression models following standardized quality control. Fixed-effect inverse-variance weighted meta-analysis was performed across datasets.

Interim analyses of 12 cohorts comprising 52,780 cases and 401,751 controls identified three genome-wide significant loci in the AMR meta-analysis. On chromosome 2, rs921876 within RANBP2 was associated with the A allele (effect allele frequency 0.62; OR = 0.96; p = 4.7 Ã— 10â »â ,). Also on chromosome 2, rs72846851 within LRP1B was associated with the T allele (effect allele frequency 0.07; OR = 1.09; p = 4.9 Ã— 10â »â ,). An intergenic locus on chromosome 13 (rs184339111) was associated with the C allele (effect allele frequency 0.03; OR = 1.20; p = 8.4 Ã— 10â »â ,).

Ongoing analyses incorporating additional datasets, local ancestry, and multivariate genomic modeling will refine association signals and strengthen ancestral representation in psychiatric genetics, advancing depression genomics in Latin America.

D36

Jolien Rietkerk M.S. Advisor(s): Roseann Peterson

Co-author(s): Madhurbain Sing, Dana Lapato, Peter Barr, Christos Chatzinakos, Tim B. Bigdeli, Kenneth S. Kendler, Hanna M. van Loo

Characterizing the polygenic profile of reproductive-related affective disorders in an East Asian population

Reproductive-related affective disorders, such as postpartum depression (PPD) and premenstrual dysphoric disorder (PMDD) are clinically significant mood disturbances that occur in relation to reproductive events and hormonal changes. Although phenotypic overlap exists across PPD, PMDD, and major depression (MD), their genetic etiological distinction remains unclear, particularly in underrepresented populations. The current study characterized and compared the polygenic score (PGS) profiles of PPD, PMDD, and MD in CONVERGE, an East Asian cohort of Han Chinese women recruited to study recurrent MD, and included assessments for reproductive-related affective disorders. Sparse whole-genome sequencing data were analyzed to estimate within-and cross-ancestry genetic correlations and to construct polygenic profiles using GCTA, LDSC, Popcorn, and PRS-CSx. The sample comprised 5,303 recurrent MD cases, including 895 PPD cases, and 5,337 screened controls without psychiatric history; among controls, 3,383 parous women were used as PPD controls. Consistent with prior literature, significant SNP-based heritability (h-SNP) was observed for PPD (h-SNP = 0.222, SE = 0.09, p = 0.009) comparable to the previously reported estimate for MD in this sample (h-SNP = 0.214 SE = 0.028, p = <10-16). Age at menarche PGS was inversely associated with risk of PPD, whereas no association was found with MD. Additionally, elevated PGS for cervical cancer was positively associated with PPD, and schizophrenia PGS predicted psychological premenstrual symptoms. Replication will be evaluated in All of Us. This ongoing work holds promise to uncover genetic interrelationships within reproductive-related phenotypes and depression in an East Asian population and examines generalizability of results across populations.

D37

Gleda Kutrolli Ph.D. Advisor(s): Roseann Peterson Ph.D.

Co-author(s): -

Cross-Ancestry Generalizability of Polygenic Risk Scores for Major Depressive Disorder in the All of Us Research Program

Polygenic risk scores (PRS) for major depressive disorder (MDD) are predominantly derived from genome-wide association studies conducted in European-ancestry populations. This imbalance raises important concerns regarding generalizability, clinical validity, and equity in precision psychiatry. Here, the cross-ancestry association of MDD PRS with depression was assessed in the All of Us Research Program.

PRS derived from large-scale meta-analytic summary statistics were applied to unrelated individuals across six genetically inferred ancestry groups. Logistic regression models evaluated associations between standardized PRS and DSM-defined lifetime MDD from the CIDI short form, adjusting for batch variables and ancestry principal components. Model performance was assessed using odds ratios per standard deviation increase, Nagelkerke RÂ², and liability-scale RÂ² assuming a 15% population prevalence.

Associations were strongest among European-ancestry participants, with Nagelkerke RÂ² reaching 7.4% ($p < 2$ Ã— 10â »Â¹â ¶). Accuracy declined in non-European ancestry groups, with intermediate explanatory power in Admixed American-like participants (up to 5.1%, $p = 1.08$ Ã— 10â »Â²Â²) and lower values in African- and East Asian-like ancestry groups (approximately 2-3%, $p = 5.60$ Ã— 10â »Â¹Â¹ & $p = 1.61$ Ã— 10â »Â², respectively). Although statistically significant associations were observed across most groups, both effect sizes and variance explained were consistently reduced outside European-ancestry-like populations.

These findings demonstrate clear ancestry-dependent gradients in PRS performance and highlight the limitations of applying predominantly European-derived genetic models across ancestral populations. Expanding representation in genomic discovery efforts will be critical to ensure equitable implementation of polygenic risk prediction in precision psychiatry.

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Interplay of Polygenic Liability, Sex, and Psychosocial Environment on Depression in Multi-Ancestry US College Students

Rationale: The relative contributions of genetic and environmental risk factors to depression may vary by sex and genetic ancestry. We investigated sex differences in how polygenic scores (PGS), interpersonal trauma (IPT), social support (SSP), and their interactions predict depression risk in a multi-ancestry cohort.
Methods: Using data from the Spit for Science cohort of US college students (N=9,668), we employed structural equation modeling to predict a latent depression factor derived from current depression symptoms. Predictors included a cross-ancestry PGS for major depression, sex, IPT, SSP, and their interactions. Models were fitted within African (21.1%), Admixed-American (12.9%), East-Asian (9.6%), European (47.7%), and South-Asian (8.6%) ancestral groups. Fixed-effect meta-analysis pooled results across ancestral groups.
Results: Sex ($\hat{I}^2$=0.43 [95%CI:0.38, 0.49]; R2=2.6%), IPT ($\hat{I}^2$=0.47 [95%CI:0.42, 0.53]; R2=3.1%), SSP ($\hat{I}^2$=-0.28 [95%CI: -0.31, -0.24]; R2=2.3%), and IPT-by-SSP interaction ($\hat{I}^2$=-0.09 [95%CI:-0.14, -0.03]; R2=0.2%) were predictors of depression. The overall PGS association was significant ($\hat{I}^2$=0.11 [95%CI:0.06, 0.16]; R2=0.3%) but not its interaction with IPT or sex. The variance explained by PGS (all predictors) ranged from 0.003% (16%) in EAS to 0.4% (23%) in AMR. Sex-stratified analyses revealed that SSP buffered IPT's association with depression in females only, suggesting a clinically actionable prevention target: for women with IPT exposure, strengthening SSP may reduce depression risk. Cross-population heterogeneity of PGS-by-SSP interaction was observed in females (I2=72.7%).
Conclusions: MDD-PGS was modestly associated, indicating that PGS is best used to supplement standard clinical assessment. Although IPT was the strongest predictor across groups, differences across populations indicate the need for universal trauma-informed prevention alongside population-specific strategies.

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SUNY Chancellor's Opportunity for Research Excellence (SCORE) in Artificial Intelligence (AI)

Given the meteoric rise in Artificial Intelligence (AI) and Machine Leaning (ML), there is an urgent need to expose healthcare students to key concepts that will prepare them to optimize the use of AI/ML in healthcare. The primary objective of SCORES-AI was to develop and implement a structured introductory workshop focused on the equitable and ethical application of AI/ML in healthcare. In 2025, SUNY Downstate launched the SUNY Chancellor's Opportunity for Research Excellence in AI as a pilot initiative designed to introduce undergraduate and medical students to AI/ ML. The curriculum included five modules: (1) foundational AI/ML terminology and concepts, including large language models (LLMs), neural networks, and deep learning; (2) a student led journal club critically evaluating AI/ML applications across healthcare settings; (3) an introduction to biostatistics, Linux, and programming for data analysis; (4) ethical considerations, including bias in AI systems; and (5) development of a research proposal integrating AI/ML methods. The SCORE program was conducted over four weeks and delivered remotely via Zoom and led by five faculty. Thirty-two students enrolled in the program, with a 100% completion rate. Formative surveys revealed that most participants had little prior knowledge of AI/ML, had previously worked with these technologies, and were unfamiliar with how AI/ML systems are applied, in healthcare systems. Students completed abstracts on a potential project that they would do applying AI/ML concepts. Most abstracts focused on advancing health equity, improving diagnostic timeliness, optimizing provider-patient interactions, and alleviating bias in AI development. Participants expressed enthusiasm for bridging medicine and technology and highlighted the importance of ethical implementation. Students' feedback indicated the need for more in-person sessions. SCORES-AI provides a model for a brief introductory course that can be augmented and replicated.