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AND EARLY CAREER RESEARCH

2024 Columbia University Postdoctoral Research Symposium

SESSION 1 | 1-2:30pm

1 **Akita, Keitaro**
Associate Research Scientist, Medicine (Cardiology)
"Prediction of Heart Failure Hospitalization in Patients with Hypertrophic Cardiomyopathy Using Plasma Transcriptomics"

Background:
Hypertrophic cardiomyopathy (HCM) often causes heart failure (HF) hospitalization. However, methods to predict HF hospitalization have not been established in HCM. Furthermore, the underlying molecular mechanisms responsible for HF hospitalization in patients with HCM remain unclear.

Objectives: To predict HF hospitalization in patients with HCM using plasma transcriptomics profiling and to determine signaling pathways dysregulated in those who subsequently experience HF hospitalization.

Methods:
In this prospective, multi-center cohort study of patients with HCM, we conducted plasma transcriptomics of 3,740 small non-coding RNAs in 375 patients with HCM. The outcome was unplanned hospitalization due to HF. We developed a transcriptomics-based model with linear discriminant analysis to predict HF hospitalization using data from one institution (training set, n=261). We tested the predictive ability in samples from the other institution (test set, n=114). Finally, we performed pathway analysis of microRNAs significantly (i.e., nominal P<0.05) predicted HF hospitalization.

Results:
During a median follow-up time of 2.6 years, a total of 37 patients in the training set (14%) and 15 in the test set (13%) subsequently experienced HF hospitalization. The area under the receiver-operating-characteristic curve of the transcriptomics-based model was 0.86 (95% CI 0.75–0.96) in the test set. The pathway analysis exhibited that the mTOR and JAK-STAT signaling pathways were significantly dysregulated in patients with HCM who subsequently experienced HF hospitalization.

Conclusions:
Our study demonstrated the ability of plasma transcriptomics profiling to predict HF hospitalization in patients with HCM. Dysregulation of the mTOR and JAK-STAT signaling pathways at baseline predicted future HF hospitalization.

2 **Álvarez-Torres, María del Mar**
Postdoctoral Research Scientist, Systems Biology
"Unveiling the functional impact of Glioma Non-Coding Germline Variants using Large Language Models"

Efforts to identify the predisposition for developing gliomas through Genome-Wide Association Studies (GWAS)1,2 face relevant challenges. These encompass difficulties in accurately pinpointing the genomic positions of germline variants, primarily found in non-coding regions, with unclear functional implications in glioma development. In this context, the GET method3, an interpretable foundation model designed to unveil regulatory grammars across 213 human cell types, emerges as a valuable tool for elucidating the mechanisms of non-coding mutations.

Our aims include: I) Validate the efficacy of the GET method using a well-documented variant and prioritize additional variants for analysis; II) Refine the genomic positions of these variants and exploring their linkage disequilibrium (LD); III) Identify potential motifs and genes that might be influenced by these high-impact variants.

After examining published GWAS, 39 germline non-coding SNPs in gliomas were found. Adding 316 variants in high linkage (R2 > 0.8) expanded the dataset to 355 variants for analysis. Using the GET method, we calculated impact scores for each variant, considering changes in motif binding score (ΔBM) and motif gradient (GM) across human adult and fetal astrocytes. We focused on rare variants (risk allele frequency <0.25) with the higher odds ratios (OR).

Using the GET method, this study overcomes the challenge of mere variant identification, aiming to establish a framework for uncovering the underlying motifs and genes susceptible to alteration. While further validation is essential, this pioneering approach shows promise in exploring the impact of germline mutations.

3 **Baranowska, Julia**
Postdoctoral Research Fellow, Medicine (Cardiology)
"Association of Sex Mismatch with Allograft Rejection after Heart Transplantation - Molecular Microscope Diagnostic System (MMDx) results"

Introduction: The effect of donor/recipient sex-matching on risk of rejection following HT is incompletely understood. We investigated the association of donor/recipient sex-mismatch with rejection assessed by MMDx after HT.

Methods: Consecutive for-cause endomyocardial biopsies performed from November 2022-August 2023 and paired MMDx results were included. Donor information was

comprehensively reviewed. Positive histology was defined as >ISHLT Grade 1R/1A or pAMR>0 and positive MMDx was defined as T-cell mediated rejection(TCMR), antibody-mediated rejection (ABMR) or mixed rejection. Histologic and MMDx results were compared based on the presence of absence of a donor/recipient sex mismatch.

Results: 159 samples from 117 HT patients were included. 63 samples (40%) were from patients who received a sex-mismatched organ: 20 F-M, 43 M-F. The median age at transplant was 50 years [38, 59]. Time from transplant to biopsy was 22 months [6-76]. 52% of patients identified as non-white.

There were no significant differences in baseline characteristics between the sex-matched and sex-mismatched groups apart from rates of induction therapy, which were higher in the sex-matched group (44% vs 21%; p=0.004). The prevalence of donor specific antibodies and previously treated rejections were similar between the groups. A positive donor-derived cell free DNA (≥0.12%) result was the most common reason for biopsy (41%), followed by symptoms (19%). Sex-mismatched hearts demonstrated no significant increase in rejection rates, as indicated by both histology (13% vs 8%; p=0.42) and MMDx (27% vs 21%; p=0.44). When stratified by MMDx rejection subtypes, sex-mismatched hearts exhibited a tendency toward a higher prevalence of antibody-mediated rejection compared to sex-matched hearts (22% vs. 11%; p=0.08).

Conclusions: In our cohort, sex-mismatched hearts were not associated with increased rates of rejection by histology or MMDx.

4 **Bedir, Nur**
Postdoctoral Research Scientist, Medicine (Endocrinology)
"PI3K Inhibition with Single Dose Alpelisib as a Model of Insulin Resistance in Healthy Adults"

The insulin resistance (IR) that underlies type 2 diabetes (T2DM) remains an elusive concept to study. Classically IR has been classified in: (1) the highly prevalent but hard to study multifactorial IR underlying T2DM, and (2) rare, pure forms, of IR arising from mutations in genes coding for the insulin receptor or autoantibodies against the insulin receptor ("insulin receptoropathies"). Patients with insulin receptor mutations, however, are extremely rare, and their metabolic phenotype is potentially complicated by developmental effects. Instead, we propose that pharmacologically inhibiting PI3K, one of the elements downstream the insulin receptor, may be a feasible method for the study of acute and reversible pure IR. This is a single-center, double-blind phase I clinical trial with patient population consisting of healthy adults ages 18-65 with body mass index 18.0-26.9 km/m2. Participants ingested a single dose of alpelisib (n = 5) or placebo (n = 6) at bedtime. The following morning, participants had blood drawn for fasting insulin and glucose levels followed by a 3-hour, oral glucose tolerance test (OGTT). Fasting plasma glucose was on average higher with alpelisib (mean ± SEM = 93 ± 6 mg/dL) vs. placebo (84 ± 2 mg/dL) (p = 0.07). Mean fasting serum insulin increased nearly fivefold: 23 ± 6 µIU/ml for alpelisib vs. 5 ± 1 µIU for placebo (p < 0.01), resulting in HOMA scores of 5.4 ± 1.4 vs. 1.1 ± 0.2 and Matsuda Index scores of 8.6 ± 2.2 vs. 3.0 ±1.6,

respectively. During the OGTT, the area under the curve (AUC) for insulin was greater with alpelisib (26.0 ± 7.5 mIU x min/ml) than placebo (5.8 ± 1 mIU x min/ml) (p < 0.02). Our results support the hypothesis that PI3K inhibition with a single dose of alpelisib is a viable method to investigate insulin resistance.

5 **Beg, Ayesha**
Postdoctoral Research Scientist, Pediatrics
*"*RpoN- Airway Itaconate Axis Regulates Pseudomonas Aeruginosa Pathoadaptation in Chronic Infections."

Pseudomonas aeruginosa (P. aeruginosa) is multidrug -resistant bacterium linked with acute pneumonia associated with sepsis and prolonged infections as seen in ventilator associated pneumonias, COPD and cystic fibrosis. Increasing antibiotic resistance has shifted the focus towards novel interventions and targets to prevent pathoadaptation and chronic infection. One potential target is the alternative sigma factor, rpoN which regulates approximately 600 genes associated with metabolism, biofilm and virulence. Genomic profiles of CF (cystic fibrosis) isolates show an accumulation of loss of function mutations in the rpoN gene and additionally reduced rpoN expression is observed in CF isolates. To mimic characteristics of a CF isolate with non-functional rpoN, the ΔrpoN mutant was studied, which successfully phenocopied biofilm lifestyle, robust infection, along with limited inflammatory response, a phenotype conducive to persistent infection. Given that ΔrpoN mutant infection accumulated increased levels of airway itaconate, a host immunometabolite, akin to pathogens adapted to" CF microenvironment", we postulated a link between this airway metabolite and rpoN regulation. In-situ chemoproteomic profiling of P. aeruginosa proteome showed covalent post-translational itaconation of cysteine at 218 of RpoN. Change in RpoN functionality via itaconate was evident through fluorescence reporter assay, which demonstrated that itaconate, but not the other airway immunometabolites succinate and fumarate, specifically attenuates RpoN function. Furthermore, we found cysteine residues available for itaconation in Klebsiella and Acinetobacter, other opportunistic pathogen that are major clinical problems. Our findings suggest that the airway metabolite itaconate reshapes host-pathogen dynamics by modulating function of pleiotropic sigma factors.

6 **Carcassi, Olga Beatrice**
Associate Research Scholar, Architecture, Planning, and Preservation
"Biofibrous 3D-Printed Earth Construction"

The use of 3D printing for earth materials is still limited to earth mixtures with minimal to no fiber reinforcement, resembling a cob-like traditional technique. Yet, recent studies show that fiber-rich earth materials such as light straw clay outperform other earth techniques in terms of their thermal performance and environmental impacts from a life cycle perspective. It is therefore critically required to expand 3D printed earth to a range of fiber-additive mixtures that increase thermal resistivity while enabling biogenic carbon storage and, potentially, enhanced ductility. This study presents an experimental assessment, developing 3D printable earth materials with maximum fiber content and linking their structural behavior to geometrical printing configuration. Part of an ongoing

line of research, this work investigates the influences of printing procedures on the structural behavior, specifically the compressive strength and stress-strain curves, for four different printing paths: control cylinder (CC), rigid weaved (RW), wisted weaved (TW) and double twisted weaving (DTW) patterns. The results demonstrate that not only the addition of fiber increases overall strength as opposed to non-fiber reinforced 3D printed earth, but also that the geometrical variation plays a critical factor in the evolution of "specific" strength. The rigid weaved pattern is shown to outperform all other geometries, presumably due to the enhanced moment of inertia along the cross section, which acts as a vertical column assemblage. The compressive strength results for the fiber reinforced 3D prints range between 2.2 and 4.3 MPa, being 2-4 times higher than shown in previous literature on 3D printed earth. The significance of this research lies in the design and development of radically low-carbon natural materials for additive manufacturing, improving material performance and applicability.

7 **Chai, Cynthia**

Postdoctoral Research Scientist, Zuckerman Institute

"Mechanisms of Drosophila Escape Circuit Evolution"

The acquisition of novel traits during species diversification enables animals to optimize their fitness in new habitats. Predation risk, which poses an imminent threat to survival and reproductive success, is a strong selective force that shapes prey behavioral repertoires and their underlying neural circuits over evolutionary timescales. In the wild, drosophilids in different habitats are challenged by different constellations of predators that employ distinct attack strategies. Although large axon-diameter giant neurons are ideal specializations for speedy escapes, they also drive uncontrolled responses, which might not always be advantageous. Depending on the approach speed of an artificial looming visual stimulus, the fruit fly Drosophila melanogaster selects between executing a faster short mode escape sequence or a slower but more stable long mode takeoff. The switch to a shorter-duration takeoff sequence is dependent on Giant Fiber(GF) interneuron activation, which can override alternate non-giant descending pathways to propel the fly out of harm's way once angular size and speed thresholds have been reached. Here, we compared the visually-evoked escape responses of D. melanogaster with its close relatives, the sibling species D. simulans and D. mauritiana. Our results indicate that, when challenged with moderately fast loom expansions, D. simulans executed the highest percentage of short mode takeoffs followed by D. mauritiana, while D. melanogaster predominantly executed long mode takeoffs. We hypothesize that species-specific differences in GF physiology and/or synaptic connectivity underlies escape mode selection variation. We are currently developing transgenic tools for cell-type-specific targeting in D. simulans and D. mauritiana to determine the neural circuit basis of escape mode selection in these non-model species. By applying an evolutionary comparative framework in the context of this behavioral neuroscience paradigm, we aim to identify the neural elements that undergo the greatest selection pressures giving rise to behavioral diversity during speciation.

8 **Chen, Miao**
Postdoctoral Research Scientist, Pediatrics
"Abnormal STAT3 Signaling in Fibroblasts Promotes Staphylococcal Growth and Abnormal Tissue Response to Infection"

Autosomal-dominant Hyper IgE syndrome due to dominant-negative mutations in STAT3 (STAT3DN) leads to infections, atopy, and connective tissue abnormalities. In addition to recurrent pyogenic pneumonia, especially due to Staphylococcus aureus, AD-HIES patients demonstrate evidence of abnormal wound healing, which includes development of pneumatoceles following infection, unexplained spontaneous bowel perforations, and non-inflammatory vascular aneurysms. Here, we developed a mouse model of infection-induced abscess and pneumatocele generation via intratracheal infection of transgenic Stat3DN Mut mice and littermate controls with S. aureus (USA300). We found that one to two weeks following infection, the Stat3DN Mut mice develop a higher rate of lung parenchymal abscesses compared to WT mice and these abscesses are more severe and larger (7/20 vs. 1/16). 4-8 weeks after l infection, large cavitary lung lesions were observed via CT only in STAT3DN mice (2/6 vs. 0/8). Moreover, S. aureus growth was significantly higher when cultured with STAT3DN fibroblasts, implying increased bacterial adhesion to cells/extracellular matrix. RNA-seq of STAT3DN dermal fibroblasts following Staphylococcal co-culture showed alterations in the expression of disintegrins and metalloproteinases involved in proteoglycan remodeling and structure of basement membranes.

Mice with STAT3 loss of function mutations provide a novel model for infection-induced pneumatocele formation, and STAT3 loss of function in fibroblasts creates a permissive environment for S. aureus growth, tissue adhesion, and impaired extracellular matrix and basement membrane remodeling. These findings may help shed light on the consequences and tissue targets of genetic and pharmaceutical alterations of the STAT3 pathway.

9 **Cheng, Qilong**
Postdoctoral Research Scientist, Applied Physics and Applied Mathematics
"Thermal Radiation Regulated Walls with Passive/Active Control for Building Envelope"

Radiative cooling (RC) is an attractive electricity-free approach to reducing energy consumption of buildings. Current RC research focuses on roofs, but limited attention has been paid to the walls, which occupy a major portion of building envelopes. Unlike the roofs that only face the sky, the walls face both the sky and the ground, so either high emissivity (high-E) or low emissivity (low E) is not the best solution. Here, we develop scalable wall designs with passive or active control to achieve regulation of thermal radiation. The passive wall with asymmetric emissivity can simultaneously reflect the thermal radiation from the hot ground and remain emissive to the cold sky in the summer, achieving temperature drops of 3.1 °C (peak) / 2.3 °C (daily average) and cooling power ~67 W m-2. This passive design can benefit 29% area and 45% population in the United States, but does not work in the cold regions due to heating penalty. To enable all-season

thermal regulation in all weather conditions, we develop a wall design with dynamic rotatable Janus fins (FinWall) to achieve tunable angular thermal emissivity on the wall surface. Field tests demonstrate that the FinWall yields a ~2.0 °C temperature elevation under cold weather and a ~3.1 °C temperature drop under hot weather, which translate to power savings of 37 W m-2 for heating and 53 W m-2 for cooling. Further building simulations indicate that a midrise apartment building equipped with FinWalls can save 24% (or 10%) annual energy versus the same building with high-E walls (or low-E walls) in the United States.

10 **Coors, Annabell**
Postdoctoral Research Scientist, Neurology
"Personality Traits and Cognitive Reserve – High Openness Benefits Cognition in the Presence of Age-related Brain Changes"

Cognitive reserve explains differential susceptibility of cognitive performance to neuropathology. We investigated whether certain personality traits underlie cognitive reserve and are accordingly associated with better cognition and less cognitive decline in the presence of age-related brain changes. We included 399 healthy adults aged 19-80 in the cross-sectional analysis and 273 in the longitudinal analyses (mean follow-up time = 5 years, SD = 0.7 years). Assessment of the BIG5 personality traits openness, conscientiousness, extraversion, agreeableness, and neuroticism was questionnaire-based. Performance in the cognitive domains of perceptual speed, memory, fluid reasoning, and vocabulary was measured with up to 24 tasks. Cognitive domain-specific brain status variables were calculated by combining up to 77 structural brain measures into single scores using elastic net regularization. Those cognitive domain-specific brain status variables explained up to 43.1% of variance in cognitive performance. We found that higher openness was associated with higher fluid reasoning and better vocabulary after controlling for brain status, age, and sex. Further, lower brain status was only associated with a greater decline in perceptual speed in individuals with low openness. In individuals with high openness, brain status was not associated with change in perceptual speed. We conclude that high openness benefits cognitive reserve.

11 **Coronel, Johana**
Postdoctoral Research Scientist, Medicine (Cardiology)
"Single-cell Characterization of Mouse Aorta during Atherosclerosis Regression"

Atherosclerosis is a cardiovascular disease characterized by the accumulation of plaque in the arteries, which restricts blood flow. Atherosclerosis is influenced by the phenotypic transitioning of smooth muscle cells (SMCs), which involves dedifferentiation, migration, and transdifferentiation into alternative cell types. SEM cells, which can differentiate into macrophages and fibrochondrocytes before reverting to their SMC phenotype, were identified in 2020. However, knowledge regarding the specific roles of SDCs in maintaining plaque stability during atherosclerosis regression is limited. Based on this knowledge gap, we propose the hypothesis that SDCs may promote plaque stability during the regression process. In this study, we used a mouse model called ROSA26 ZsGreen1+/+; Ldlr−/−; Myh11-CreERT2, which allowed us to trace the lineage

of smooth muscle cells (SMCs). At 6 weeks of age, the mice were administered a tamoxifen diet for 1 week, followed by a week of regular chow diet. Subsequently, mice were subjected to a 16-week Western diet to induce atherosclerosis. Afterward, the mice were administered HDAd-LDLR and a chow diet at 0, 2, 5, 10, and 20 weeks to initiate the regression of atherosclerosis. Arterial tissues, such as the ascending aorta, BCA, and thoracic aorta with atherosclerotic lesions, were disintegrated into individual cells and then sorted by fluorescence-activated cell sorting (FACS). Single-cell RNA sequencing (scRNA-seq) was performed, and no modifications were detected in the smooth muscle cell clusters (SMCs). Conversely, we noted an increase of two fibroblast clusters characterized by heightened proliferation and reduced apoptosis and senescence. Conversely, the number of macrophages within the plaques decreased, whereas collagen levels were elevated and ticker fibrous caps. In general, as this is an ongoing project, we will assess whether one or both fibroblast clusters are necessary for the stabilization of plaques during the regression of atherosclerosis.

12 **Dias Gurjao, Carino**
Postdoctoral Research Scientist, Medicine (Hematology & Oncology)
"Single Analyte Profiling of the Mutational, Immune and Microbiome Landscape in African American Colon Cancer Patients"

Colorectal cancer (CRC) increases in incidence and disproportionately affects African American (AA) patients who have worse outcomes. Yet molecular profiling in this population is scarce. Here, we performed whole-exome sequencing (WES) of 356 immediately snap-frozen tissues comprising AA CRC and matched, distant normal colon and identify distinct genomic drivers, DNA signatures, and, surprisingly, mosaic pathogenic mutations that are not present in the patient-matched CRC. We inferred T cell infiltration and tissue-resident microbiome (TR-M) directly from WES, enabling integrative analyses. Compared to normal colon, T cell infiltration is strongly decreased in tumours with microsatellite stability (MSS), while microsatellite unstable (MSI) and POLE mutant tumours had similar levels, indicating that immune evasion in MSS rather than increased T cell infiltration in MSI/POLE-mutants occurs. Analysis of matched normal/tumour tissues revealed the evolving TR-M at unprecedented granularity and identified distinct niches of interactions with genomic and tumour-microenvironmental features. Together, this study represents the largest comprehensive genomic analysis of CRC in AA and provides a framework for performing a multi-layered analysis from a single analyte, thus, affording a cost-effective approach to expedite medical discoveries in underrepresented ancestries.

13 **Elkefi, Safa**
Postdoctoral Research Scientist, Nursing
"Factors Associated with Post-treatment Smoking among a Diverse Sample of Cancer Survivors"

This study aims to explore the prevalence of post-treatment smoking among cancer survivors and examine the association between smoking behavior and various demographic, psychosocial, and health perception factors. We utilized cross-sectional

data from the Health Information National Trends Survey (HINTS) collected between March and November 2022. Socio-demographic, psychosocial (mental distress, social isolation, and meaning and purpose in life), and health perception variables were assessed as correlates of smoking status. Descriptive statistics and logistic regression analyses were employed for analysis. Most of the participants were over 65 years old, females, and identified as Whites. Lower socioeconomic status (education and income) was associated with higher rates of post-treatment smoking. Elevated levels of mental distress and social isolation were significantly associated with smoking. At the same time, a greater sense of meaning and purpose in life was linked to a lower likelihood of smoking. Moreover, positive health perceptions and confidence in managing health were inversely and significantly related to smoking behavior. Although smoking is risky, some cancer survivors report current smoking. As such, providers should continue to assess smoking status and facilitate smoking cessation treatment among cancer survivors. Mental health and psychosocial factors were identified as key risk factors for persistent smoking and should be considered in future initiatives to reduce smoking among cancer survivors.

14 **Erol, Betul**
Postdoctoral Research Scientist, Pediatrics
"Functional Genomics of Human Obesity"

Obesity is a complex trait influenced by multiple genetic and environmental factors. Recent advances in genome-wide association studies (GWAS) have led to the identification of approximately 12 million single nucleotide polymorphisms (SNPs) that are associated with body mass index (BMI), an established proxy for measuring adiposity in population studies. These SNPs have been mapped to over 1000 genomic loci, providing a broad landscape of the genetic architecture underlying BMI variability.

One of the critical questions that arise from these findings is understanding the specific cell types in which these SNPs exert their functional impact. Furthermore, elucidating the target genes of these SNPs is pivotal for revealing the molecular mechanisms through which they influence BMI.

Among the diverse populations of neurons in the brain implicated in the regulation of feeding and energy balance, POMC neurons are the major appetite-suppressing neurons in the arcuate nucleus of the hypothalamus. Thus, dissecting the influence of BMI-associated SNPs in POMC neurons could serve as a starting point to unravel the complex genetic networks that regulate body weight.

15 **Faina, Peterson**
Postdoctoral Research Scientist, Climate School
"How Wet is 'Wet': Comparing Pluvials in Southern Madagascar"

Madagascar experienced a dramatic turnover of vertebrate species between 1200 and 700 cal BP affecting ~40 endemic species, some replaced by invasive, human-introduced taxa. In the subarid spiny thicket (ST) ecoregion of the southwest, climate change (slow drying after 2000 BP followed by a severe, prolonged drought between 1600 and 900 BP)

appears to have played a triggering role. There is little evidence of early human impact. In contrast, vertebrate population collapse began under wetter conditions in the dry deciduous forests of the northwest, with strong evidence of human agency. To better understand the roles of climate change and human activities, particularly in the ST, we documented the climate and vegetation history of this region prior to and after the arrival of humans. We studied the stable carbon and oxygen isotopes of 11 stalagmites from the ST covering the past 70,000 years. Throughout this time, the ST was consistently dry (likely drier than other parts of Madagascar), and changes in rainfall were correlated with changes in vegetation. Even during the apparently wettest periods, severe and sometimes prolonged droughts occasionally occurred. Some droughts extended well north of the ST, while others did not. The drought between 1600 and 900 BP was, by no means, the most severe, nor was it the most geographically expansive. However, this drought appears to have made large endemic species more vulnerable to subsequent human activities and may have triggered an earlier and more rapid collapse of vertebrate populations in the ST.

16 **Feng, Meng**

Postdoctoral Research Scientist, College of Dental Medicine

"Mechanosensitive Piezo1 Activates YAP/TAZ/CCN1 Signaling to Promote Cartilage Resident Mesenchymal Stromal Cell Aging in Knee OA Development"

Introduction: Varus malalignment and aging increase the susceptibility of cartilage to mechanical overloading, which stimulates catabolic metabolism through the YAP/TAZ/CCN1 pathway to break down the extracellular matrix and lead to knee osteoarthritis (OA) and joint pain. We previously identified CD166+ OA-MSCs in OA cartilage. We also reported that high tibial osteotomy (HTO) could shift the mechanical overloading from an imbalanced status to a neutral alignment and contribute to endogenous cartilage regeneration. However, the underlying mechanisms of physical loading on endogenous cartilage stabilization and regeneration after HTO remain unclear. We hypothesized that OA-MSCs aging was reversed by mechanical off-loading and promoted endogenous cartilage repair in a healthy biomechanical environment due to the inhibition of mechanoresponsive Piezo1/YAP/TAZ/CCN1 signaling.

Methods: This study was approved by IRB at Xi'an Jiaotong University and Columbia University. Patients with medial compartment OA (52.75±6.85 yrs, left knee 18, right knee 20) underwent open-wedge HTO by the same surgeons at one single academic sports medicine center from April 2019 and April 2023. Radiographic images were collected with a minimum of 24 months of follow-up. Joint space width (JSW) was measured by uploading to ImageJ software. The Knee injury and Osteoarthritis Outcome Score (KOOS) toolkit was applied to assess the pain level. Outerbridge scores were obtained from a second-look arthroscopic examination. RNA was extracted to quantify catabolic targets and pro-inflammatory genes. RNA-sequencing was applied to identify the potential role of Piezo1 /YAP/TAZ/CCN1 signaling in cartilage aging. SiRNA and Yoda1 were treated in OA-MSCs to knock down or activate Piezo1. Immunofluorescence, IHC, and Western blotting were used to probe the expression of YAP/TAZ/CCN1. Student's t-test for two group comparisons was utilized.

Results: To understand the role of mechanical loading-induced cartilage repair, we measured the serial changes in joint space width (JSW) after HTO. Our data showed that HTO increased the JSW, decreased the VAS pain score, and improved the KOOS function score significantly. We further scored cartilage lesion severity using the Outerbridge classification under a second-look arthroscopic examination while removing the HTO plate. It showed the cartilage lesion area decreased significantly, the full thickness of cartilage increased and mechanical strength was better compared to the pre-HTO baseline. HTO dampened medial tibiofemoral cartilage degeneration and accelerated cartilage regeneration from Outerbridge grade 2 to 3 to Outerbridge 0 to 1 compared to untreated varus knee. It suggested that HTO induced-physical loading was involved in cartilage regeneration. SiRNA treatment knocked down Piezo1 and YAP/TAZ/CCN1 at the protein level, however, Yoda1 treatment activated Piezo1 and facilitated the translocation of YAP from cytoplasm to nucleus to upregulate YAP/TAZ/CCN1 in aged OA-MSCs. HTO-induced neocartilage showed decreased expression of Piezo1, YAP, TAZ, RUNX2, COL10, CCN1 and increased SOX9 in human knee. RNA-sequencing of OA-MSCs indicated that catabolic activities (YAP, TAZ, RUNX2, COL10, CCN1) were down-regulated in response to physically mechanical loading under 3-dimensional culture. Lastly, we found that physical loading and siRNA treatment of Piezo1 inhibited catabolic markers (IL-1 and IL-6) and increased anabolic markers (SOX9, COL2) in vitro.

Conclusion: Knee-preserved HTO intervention alleviates varus malalignment-related knee joint pain, improves daily and recreation function, and repairs degenerated cartilage of medial compartment OA. The off-loading effect of HTO may rejuvenate OA-MSCs aging and promote endogenous cartilage regeneration by inhibiting mechanosensitive Piezo1/YAP/TAZ/CCN1 signaling.

17 **Florez-Paz, Danny**
Associate Research Scientist, Neurology
"Classical Complement-Dependent and Independent Mechanisms in the Elimination of Inappropriate Synapses of Sensory-Motor Circuits"

Normal movement requires the proper assembly and function of sensory-motor circuits in the spinal cord. Although their assembly transpires during embryonic development, their development and refinement occur postnatally. Proprioceptive sensory neurons form synapses only with homonymous and synergistic motor neurons in mature circuits. Yet, previous reports suggested the presence of inappropriate proprioceptive synapses on motor neurons from antagonistic muscles during embryonic development.
Here, we demonstrate that inappropriate synapses are initially formed and subsequently eliminated. We also shed light on the molecular mechanisms involved in this process. We previously reported that C1q, may be involved in the elimination of excessive proprioceptive synapses during postnatal development. However, is unknown whether this synaptic elimination impacts the refinement of sensory-motor circuits including the elimination of inappropriate synapses.

To address this, we studied the role of C3, a downstream protein in the classical

complement, known as “eat me signal” for synapse removal. Using virally-mediated map strategies together with genetic removal of C3 in mice, we found a broad increase of proprioceptive synapses and confirmed the incidence of inappropriate proprioceptive synapses on motor neurons from antagonistic muscles. Using the spinal cord-hindlimb preparation ex vivo and patch clamp intracellular recordings we verified that these synapses were functional. To investigate whether synapses that are destined to be eliminated can be protected, we tested whether CD47 - a protein reported as a “don’t eat me signal” in brain circuits - can confer any synaptic protection. Strikingly, genetic removal of CD47 in mice, had a similar effect to that observed in C3-/- mice, indicating that CD47 plays a different and unexpected role to that reported in the developing brain, acting as an “eat me signal” for synapses destined to be removed.

Together, our results demonstrate that inappropriate synapses are eliminated in sensory-motor circuits through classical complement-dependent and independent molecular mechanisms during early spinal cord development.

18 **Ge, Jian**
Associate Research Scientist, Medicine
“Deciphering the Role of Dicer in Tracheal Basal Cell Regeneration Post-Polidocanol Induced Injury”

The regeneration of tracheal epithelium after injury is a complex biological process essential for the repair of the respiratory tract. This study investigates the effect of Dicer on the proliferation and differentiation of basal cells, following the ablation of the trachea's pseudostratified epithelium. Dicer, known to be crucial for embryonic lung branching and the survival of basal cells, is surprisingly not expressed in the basal cells of the adult trachea, as single-cell RNA sequencing has revealed. Our research employs an inducible Dicer deletion model in adult mice to assess its impact on tracheal regeneration after polidocanol injury. We found that although polidocanol injury leads to basal cell hyperplasia, mice with a Dicer mutation experienced an arrest in basal cell proliferation during the early post-injury stages, with a significant deficiency in basal cell numbers even after the epithelium had structurally recovered. This observation highlights Dicer's critical role in the proliferative phase of basal cell regeneration, without influencing their ability to differentiate. Further investigation, through bulk RNA sequencing of regenerated tracheal basal cells from both wildtype and Dicer-mutant mice three days post-injury, aims to identify the transcription factors and signaling pathways that facilitate early basal cell regeneration. This could provide new insights into the processes of tracheal repair and identify potential therapeutic targets to enhance epithelial regeneration following injury.

19 **Hasanzadeh, Fatemeh**
Postdoctoral Research Scientist, Neurology
“Toward Finding the Neural Implementation of Cognitive Reserve:
A Longitudinal Analysis of Task Switching”

Aging is associated with changes in brain structure and executive functions, particularly

in tasks involving cognitive flexibility, such as task switching. However, substantial individual differences in the degree of cognitive impairment indicate that some individuals can cope with brain changes more effectively than others, suggesting higher cognitive reserve (CR). To find a neural implementation of CR, the longitudinal relationship between task-related activation, structural brain changes, and cognitive performance during an executive task-switching paradigm was examined. Switch cost was measured as change in reaction time from non-switch to switch condition. Participants of this study includes 96 older individuals who were assessed at baseline and followed up after five years.

Multivariate structural brain measure at baseline and 5-year follow-up were quantified using an autoencoder technique integrating cortical volume, cortical thickness, and white matter, and hyperintensities into a brain structural index. Task-related activation was measured using ordinal trends canonical variate analysis (OrT CVA), which detects patterns with increased activation from non-switch to switch conditions. Differential task-related fMRI activation (dOrT) was calculated as the difference in pattern expression scores between non-switch and switch conditions at baseline. A linear mixed model tested whether dOrT moderated the impact of brain alterations on switch cost over a 5-year period.

There was a significant interaction between brain index and dOrT on switch cost, demonstrating a moderation effect of task-related activation. Higher differential task-related activation buffered the impact of brain structural measures on rising switch costs, enabling older adults to cope with age-related structural decline and preserve cognitive flexibility. The results demonstrate that obtained task-related activations are a neural implementation of CR and may have implications for interventions targeting neural resilience factors to decrease age-related cognitive declines.

20 **Hasselluhn, Marie**
Postdoctoral Research Scientist, Medicine
"Disrupting Local Immunosuppression by Combined myCAF/Myeloid Targeting in Pancreatic Cancer"

Local immunosuppression (LIS) is one of the striking hallmarks of pancreatic ductal adenocarcinoma (PDAC) due to the combined effects of multiple immunosuppressive cell types in the tumor microenvironment (TME). There is great need for an increased understanding of the cellular crosstalk within tumors to understand how stromal cells coordinate in their suppression of immune responses. Here we examine the interactions of myofibroblastic cancer-associated fibroblasts (myCAFs) and myeloid cells and how they coordinate to suppress immune responses in the PDAC TME.

We interrogate PDAC stromal cell biology by using targeted therapies to perturb various cell populations both in vivo using genetically engineered mouse models, and ex vivo using tumor explants. Explants are short-term slice cultures that enable experimental study of intact tumor sections with a full complement of cell types. Importantly, explants maintain their histopathological architecture and cellular diversity over time. This

medium-throughput platform allows for testing of multiple drugs and mechanistic hypotheses in the native PDAC TME.

We demonstrate that Smoothened inhibition (SMOi) decreases the proliferation and activity of myCAFs, but provokes the expansion of CD11b-positive myeloid cells in vivo. Thus, we hypothesize that LIS in PDAC is maintained by a balance between myCAFs and myeloid cells, preventing effective T cell invasion. Single cell RNA-seq data comparing ctrl vs. SMOi-treated PDAC elucidates stromal subpopulations involved in the LIS phenotype and guides the identification of myeloid subtypes emerging after SMOi. Strikingly, we demonstrated that simultaneous SMOi and targeting myeloid cells via anti-Gr1 or CCR1 inhibition significantly elevates cytotoxic T cell numbers.

In summary, we are elucidating the complex mechanism behind LIS in PDAC by employing our novel explant culture system alongside in vivo studies. We aim to develop a translatable regimen to neutralize LIS, reactivating the cytotoxic T cells in the tumor periphery to invade, proliferate, and attack cancer cells.

21 **Hu, Boyi**
Postdoctoral Research Scientist, Neurology
"A Longitudinal Semi-Parametric Approach for Outcome-Guided Disease Subtyping using High-dimensional Omics Data"

Primary challenges to treating and preventing neurodegenerative diseases include extensive heterogeneity in the clinicopathologic state of older individuals, suggesting the presence of subgroups of individuals who share certain biological features but respond differently to risk factors of the disease. The combination of high-throughput sequencing technology and conventional unsupervised clustering methods has been employed to identify subgroups of individuals who share similar patterns in genomic features to define disease subtypes. The resulting clusters, however, may not capture clinically meaningful disease subtypes because certain confounder factors (e.g., demographic factors) can dominate the clustering procedure and identify clusters may not relate to disease clinical outcomes. To identify disease subtypes guided by a clinical outcome, existing methods, such as supervised clustering, uses mixture models that primarily focus on time-invariant clinical outcomes. In this talk, we will propose a novel latent generative model that incorporates clinical outcomes and covariates measured over time, aiming to identify outcome-guided disease subtypes from longitudinal clinical data and high-dimensional omics data. Our approach is designed to enhance the resulting subtypes in relation to the disease clinical outcome of interest. The method will incorporate genetic pathway information to regularize variable selection and enhance interpretability. The proposed method will be applied to Alzheimer's disease of older adults with transcriptomic profiles and longitudinal clinical data to identify clinically relevant disease subtypes and to pinpoint genes that define these subtypes. Through a special construction, we will also test gene by cardiovascular risk factor interaction. This work is crucial for the design of therapeutics and trials that focus on precise molecular targets that can be better tailored to individuals.

22 **Hwang, Youngmin**
Postdoctoral Research Scientist, Medicine
"FGF2 Promotes the Expansion of Mesothelial Cell Progenitor Pools Expansion and Inhibits BMP4-mediated Cell Fate Change into Smooth Muscle Cells"

Mesothelial cells, lining the external layer of the body wall and internal organs, are important for development and homeostasis. Although the unusual proliferation of these cells—often exacerbated by asbestos exposure—can cause mesothelioma by co-opting developmental pathways, our understanding remains scant regarding the key signaling processes that oversee the self-renewal, maturation of mesothelial progenitor cells (MPCs), and their differentiation into smooth muscle cells (SMCs) during development.

Here, we established a highly efficient protocol for culturing WT1+ MPCs isolated from the porcine thorax. We performed RT-qPCR and immunofluorescence to analyze the signaling pathways critical for MPC self-renewal, proliferation, maturation, and differentiation into α-SMA+ SMC. Treatments to MPC with ascorbic acid and BMP4 were found to boost not only MPC self-renewal but also their cellular differentiation into SMC. We found that calretinin (CALB2), a matured mesothelial cell marker, was expressed in the mesothelium and neighboring lung mesenchyme from the canalicular to the alveolar stage of developing porcine lungs, while scRNA-seq analysis of developing human lung revealed mesothelin (MSLN) expression from the late pseudoglandular stage. FGF2 initiated the MPC maturation into MSLN+ cells but not CALB2+ cells, while CHIR99021 (CHIR), a Wnt activator, Retinoic acid, and Sonic Hedgehog (Shh) efficiently induced CALB2+ maturated mesothelium. Interestingly, FGF2 and PDGF promoted the WT1+ MPC pool expansion and blocked BMP4-mediated SMC differentiation, while only FGF2, but not PDGF, sustained WT1+ MPC pool expansion for long-term culture, suggesting that the PDGF effect on the MPC expansion is limited. Our results indicated numerous signaling are intertwined in MPC self-renewal, step-wise maturation, and cell fate change. Among them, FGF2 emerges as a unique developmental pathway, mainly Inducing WT1+ MPC pool expansion at the pseudoglandular stage and obstructing BMP4-induced MPC differentiation into SMC, offering promising therapeutic insights for mesothelioma carcinogenesis initiation.

23 **Jin, JianJun**
Postdoctoral Research Scientist, Ecology, Evolution, and Environmental Biology
"Traversome: a Graph-based Likelihood Model for Pangenome Assembly and Variant Relative Frequency Estimation from Mosaic Samples"

A bulk DNA sample can exhibit mosaicism for several reasons, ranging from mutational variation among cells within a single multicellular individual, to variation among multiple genomes pooled together from two or more multicellular, unicellular, or acellular individuals. An assembly graph constructed from bulk genome data, depicting the connections between contigs, often harbors ambiguity regarding the scaffolding of these contigs, stemming from both repetitive sequences within individual variants and mosaicism across variants. Consequently, disentangling the graph to isolate each genome individually emerges as the primary challenge in genome assembly. Current genome

assemblers typically collapse mosaic variants into one or two best estimates, resulting in either chimeric assembly errors or the loss of low frequency variants. Here, we introduce an alternative approach that enables disentangling and assembling multiple genomes from a mosaic DNA sample separately and estimating their relative frequencies. We derive a new likelihood framework for comparing genome variant sets assembled from mosaic DNA samples based on the distribution of traversal paths of long reads mapped to an assembly graph, with mapping positions modeled as multiple multinomial probabilities densities. Our approach is implemented in the new pangenome assembly tool Traversome. We demonstrate Traversome using both simulated mosaic DNA samples as well as empirical datasets from bacteria and organelles of plants. Traversome exhibits similar accuracy to other assemblers in the absence of mosaicism, but much greater accuracy when genome variants are present. By treating DNA mosaicism as a default expectation, Traversome transforms genome assembly into a pangenome assembly process. Our tool and novel graph-based likelihood algorithm provide a major advance for identifying and analyzing chromosome-scale genome variants.

24 **Kelestemur, Taha**

Associate Research Scientist, Anesthesiology

"Adenosine Metabolized from Extracellular ATP Ameliorates Organ Injury by Triggering A2BR Signaling"

Background: Trauma and a subsequent hemorrhagic shock (T/HS) result in insufficient oxygen delivery to tissues and multiple organ failure. Extracellular adenosine, which is a product of the extracellular degradation of adenosine 5' triphosphate (ATP) by the membrane-embedded enzymes CD39 and CD73, is organ protective, as it participates in signaling pathways, which promote cell survival and suppress inflammation through adenosine receptors including the A2BR. The aim of this study was to evaluate the role of CD39 and CD73 delivering adenosine to A2BRs in regulating the host's response to T/HS.

Methods: T/HS shock was induced by blood withdrawal from the femoral artery in wild-type, global knockout (CD39, CD73, A2BR) and conditional knockout (intestinal epithelial cell-specific deficient VillinCre-A2BRfl/fl) mice. At 3 three hours after resuscitation, blood and tissue samples were collected to analyze organ injury.

Results: T/HS upregulated the expression of CD39, CD73, and the A2BR in organs. ATP and adenosine levels increased after T/HS in bronchoalveolar lavage fluid. CD39, CD73, and A2BR mimics/agonists alleviated lung and liver injury. Antagonists or the CD39, CD73, and A2BR knockout (KO) exacerbated lung injury, inflammatory cytokines, and chemokines as well as macrophage and neutrophil infiltration and accumulation in the lung. Agonists reduced the levels of the liver enzymes aspartate transferase and alanine transaminase in the blood, whereas antagonist administration or CD39, CD73, and A2BR KO enhanced enzyme levels. In addition, intestinal epithelial cell-specific deficient VillinCre-A2BRfl/fl mice showed increased intestinal injury compared to their wild-type VillinCre controls.

25 **Khatiwada, Prabesh**

Postdoctoral Research Scientist, Medicine (Immunology)

"Enhancing Adoptive Immunotherapy: Targeting EBV Oncoproteins with Immunosuppression Resistant Cytotoxic Th1/17-like CD4+ T Cells"

Hypothesis: We hypothesized that ex vivo expansion of peripheral blood (PB) derived CD4+ T cells targeting Epstein-Barr Virus (EBV) oncoproteins under type 17 polarizing conditions might generate highly active T helper cells displaying enhanced cytotoxic anti-tumor properties, concurrently retaining robust proliferative capacity and stem-cell-like self-renewal properties critical for the successful eradication of EBV-driven malignancies in vivo. We also hypothesized that type 17 inflammatory cytokines might poise the immune effectors towards resistance to the immunosuppressive effects of tacrolimus via enhanced Multi-Drug Resistance 1 (MDR1)-driven efflux.

Background: EBV establishes a lifelong asymptomatic infection in the host post-initial Immune clearance often occurring in early childhood. Alterations in the immune surveillance in subjects with impaired cellular immunity can lead to viral reactivation and uncontrolled B-cell lymphoproliferation manifesting as post-transplant lymphoproliferative disease (PTLD) and malignant transformation into B-cell lymphomas and some epithelial tumors, conditions frequently seen in recipients of solid organ transplants (SOT). Adoptive transfer of virus-specific cytotoxic T cells targeting EBV surface antigens LMP1 and LMP2A (EBV-CTLs) has shown promise in EBV latency II and III associated malignancies such as PTLD. The efficacy has been limited by the suboptimal potency of donor-derived EBV-CTLs and limited in vivo persistence and activity, particularly in targeting Latency I-associated diseases like PTLD where only the expression of EBNA1, an HLA II restricted EBV oncoprotein, is retained. Moreover, the activity of the currently used EBV-CTLs is likely hampered by immunosuppressive drugs (e.g. tacrolimus) Building upon our prior research on Th1/17 polarized CD4+T cells' capacity to eradicate large tumors and, exhibit enhanced self-renewal and stem cell-like properties, we aimed to explore whether proinflammatory conditions conducive to Th1/17 like CD4+T cells could offer a more effective strategy for targeting EBV across all latency stages.

Methods: We developed a method for generating novel and highly potent CD4+ cytotoxic T cells (CD4+-CTLs) targeting three major EBV antigens, EBNA1, LMP1, and LMP2A simultaneously. Peripheral blood mononuclear cells (PBMCs) were isolated from healthy donors, and either total T cells or CD4+T cells were purified. These cells were then stimulated with PBMCs loaded with overlapping peptide libraries spanning LMP1, LMP2A, and EBNA1 antigens, either under neutral conditions (Th1-CD4+-CTLs) or in the presence of pro-inflammatory (Th1/17-CD4+-CTLs) cytokines ex vivo for 12-14 days. The phenotypes, reactivity, and cytotoxic capability of these CD4+-CTLs against autologous EBV-Lymphoblastoid cell lines (LCLs) were assessed in vitro and in vivo upon adoptive transfer into tumor-bearing NSG mice. The expression of MDR1 was evaluated by flow cytometry and T-cell functionality in the presence of tacrolimus was tested upon antigenic stimulation.

Results: In comparison to EBV-CTLs generated from PBMCs or total T cells, Th1/17-CD4+-CTLs exhibited a significantly higher antigen-specific reactivity with a marked skewing towards EBNA1 antigen, and displayed marked polyfunctionality, concurrently secreting TNF-α, IFN-γ, and inducible GzmB, while maintaining IL-2 secretion. This reactivity and polyfunctionality were markedly enhanced upon the second round of expansion in Th1/17-CD4+-CTLs, whereas the potency of Stim 2 Th1-CD4+-CTL tended to diminish, suggesting functional exhaustion. Antigen-reactive Th1/17-CD4+-CTLs contained a significant central memory (TCM) (CCR7hi, CD27hi) and resident memory (TRM) (CD103hi, CD69hi) phenotype, while Th1-CD4+-CTLs predominantly displayed an effector memory (TEM) phenotype and lack of CD103. Furthermore, type 17 priming induced the expression of MDR1, correlating with enhanced resistance to the suppressive effect of tacrolimus at typical therapeutic levels. Th1/17-CD4+-CTLs demonstrated enhanced cytotoxicity against autologous EBV-LCLs and superior proliferative capacity upon antigenic stimulation in vitro, whereas Th1 CD4+-CTLs proliferated poorly. In an adoptive transfer experiment using NSG mice inoculated systemically with EBV-LCL line, Th1/17-CD4+-CTLs caused a significant reduction/elimination of LCL tumor burden when compared to Th1-CD4+-CTLs, correlating with superior self-renewal and persistence of the Th1/17-CD4+ CTL.

Conclusion: Our data demonstrate that ex vivo expansion of CD4+ EBV-CTLs can be markedly improved in the presence of type 17 polarizing cytokines, generating highly active immune effectors with enhanced antigen-specificity, polyfunctionality, high proliferative capacity, and self-renewal potential, displaying superior in vivo persistence and anti-tumor activity in a humanized model of EBV-PTLD. Importantly, Th1/17 CD4+ EBV-CTLs express MDR1, an efflux pump with broad specificity known to increase resistance to calcineurin inhibitors, suggesting that Th1/17 EBV-CTLs might be more active in actively immunosuppressed patients with PTLD. These results offer considerable potential for advancing adoptive immunotherapies to combat EBV-associated diseases and suggest broader applications for targeting other viral oncoproteins.

26 **Konstantinovsky, Daniel**
Postdoctoral Research Scientist, Chemistry
"A Machine-learning / Physics-based Solution to Dynamic Drug Binding"

Despite significant advances in computational drug discovery in recent years, protein drug targets involving highly dynamic elements such as loops remain challenging due to the difficulty of accurately predicting the structure of these elements in the presence of ligands with widely varying structures and chemistries. Predicting the structure of a target with and without the ligand is necessary to assess the potency of a drug candidate, and so is essential to the drug discovery process. Despite their impressive performance overall, tools such as AlphaFold2 remain unable to reliably predict ligand-bound protein conformations at atomic resolution, especially when the target has no counterparts in the training data. Our group has been focusing on the most difficult cases involving large conformational changes and highly dynamic structural elements including long loops. We are developing a machine-learning based solution for flexible refinement of ligand-bound

structures coming out of other prediction methods such as induced fit docking molecular dynamics (IFD-MD). Our method, which is based on the autoencoder model, is able to combine the best features of multiple candidate structures to produce better output structures. It manipulates multiple regions at once, including the ligand itself. Rather than training on the entire proteome, we train our model on one system at a time to ensure that all relevant features are captured. Our method is completely general and can refine any protein or protein-ligand system. We use a highly accurate implicit solvent model to score output structures before testing them further with free energy perturbation (FEP).

27 **Kumar, Vijay**
Postdoctoral Research Scientist, Environmental Health Sciences
"A Simulation Study Analyzing the Impact of Differential Exposure Measurement Error of Air Pollution on Preterm Birth"

Background: Personal exposure to air pollutants is often unknown, introducing measurement error due to reliance on predicted concentrations and lack of information on individual's activity patterns. Studies have quantified and corrected for non-differential exposure measurement error, i.e., the error is not expected to depend on the true outcome status, in health analyses. Recently, there is an increase in the accessibility of daily air quality data, including warnings during air pollution episodes or wildfires, potentially leading to change in behavior, especially among certain vulnerable subgroups (e.g., pregnant people), leading to potential differential exposure measurement error. We examined the impact of differential exposure measurement error on the well-known association between air pollution and preterm birth (PTB).

Methods: We investigated the impact of differential exposure error on PTB in a simulation study. We generated data based on empirical distributions of daily PTB and fine particle (PM2.5) concentrations in New York City (2006-2016). We examined the impact of varying levels of both non-differential and differential error on the estimated rate ratios.

Results: In the examined scenarios of different error levels, differential error predominantly introduced bias towards the null. and the magnitude of this bias depended on the distribution of error. For example, in higher levels of error, the bias ranged between -73% and -27%. In cases of simulated null associations, differential error did not induce associations.

Conclusion: As air pollution warnings and air quality information become increasingly prevalent, our analysis highlights the importance of characterizing the impact of differential measurement error, emphasizing the need for a comprehensive understanding of error dynamics in air pollution and PTB studies.

28 **Lai, Yunjia**
Postdoctoral Research Scientist, Environmental Health Sciences
"Untargeted Metabolomics Discovers Ameliorative Molecules for Manganese-induced Parkinson's Disease Phenotypes and Neurotoxicity"

Parkinson's disease (PD) is the most common motor disorder in the US and worldwide. PD cases over age 65 are largely sporadic, with accumulative data suggesting a predominant etiologic role of environmental factors over genetics. Chronic exposure to manganese (Mn), occupational or environmental, has been widely associated with PD. Mn toxicity itself manifests as a disease termed manganism, sharing strikingly common neurodegenerative hallmarks with PD. However, the mechanistic basis linking the two remains unclear, and disease-modifying therapeutics for PD are lacking. In this study, we aim to identify molecular pathways underpinning Mn-induced parkinsonism and to discover therapeutic targets for manganism and potentially for PD. To accomplish this, we developed an adult in vivo model (Drosophila melanogaster) of Mn toxicity to recapitulate PD hallmarks, conducted untargeted metabolomics to identify key biochemical modulators before motor symptoms surfaced, and tested the therapeutic potential of key metabolites in ameliorating Mn-induced toxicity and parkinsonism. Results demonstrated successful phenotypic recapitulation, spanning dose-dependent lifespan reduction, deficits in climbing and locomotor behaviors, dopaminergic neuronal loss, and mitochondrial dysfunction. Metabolomics analyses identified distinct dose-specific patterns as revealed from the multivariate partial least square discriminant analysis (PLS-DA). Welch's t-test comparing high dose (30 mM) and control vehicle singled out statistically significant molecular features between groups. Cheminformatics identified 234 and 405 metabolites respectively differentiated in heads and bodies. The perturbed brain metabolomes embraced a vast chemical space, spanning from vitamins (e.g., B family), lipids (e.g., acylcarnitines, sphingolipids, ceramides, lysophospholipids, fatty acids), amino acid neurotransmitters (e.g., arginine, glutamine/glutamate), to purines (e.g., adenine). Quantitative pathway enrichment analyses (qMSEA) and intercompartmental comparison determined biotin metabolism as a master pathway underpinning Mn toxicity with highest pathway enrichment and systemic body–brain increases in Mn-treated groups compared to controls. Rescue trials in vivo and human iPSC-differentiated neurons confirmed biotin as a countermeasure against manganism and PD.

29 **Laughney, Caitlin**

Postdoctoral Research Fellow, Psychiatry

"Child Sexual Abuse as a Predictor of Specific and Cumulative Forms of Stigma-Related Victimization among Transgender Adults in the United States"

Compared to cisgender individuals, transgender people disproportionately experience high rates of violence across multiple contexts throughout the life course. Child sexual abuse (CSA) has been associated with specific and cumulative forms of violence among the general population, however, these associations have not been examined among transgender adults. This study tests possible associations between CSA victimization and specific and cumulative forms of hate crimes and stigma-related victimization among transgender adults. A national probability sample of transgender adults (U.S. Transgender Population Health Survey, 2016-2018) was used for this cross-sectional secondary analysis (N=274). CSA was measured using the child sexual abuse subsection of the Center for Disease Control's Behavioral Risk Factor Surveillance System Adverse

Childhood Sexual Experience module (CDC BRFSS ACE). Adult experiences of enacted stigma were measured using six questions that assessed experiences of criminal victimization, harassment, and threats. Nearly half (45%) of transgender adults in our sample reported having experienced CSA victimization, and 40% reported experiencing four or more types of stigma-related forms of victimization as an adult. Compared to transgender adults who have never experienced CSA, transgender adults who had experienced CSA victimization were significantly more likely to have been assaulted, threatened with violence, verbally abused, and assaulted with an object as an adult. Transgender survivors of CSA were also significantly more likely to have experienced four or more forms of stigma-related violence as an adult compared to transgender adults who have never experienced CSA. Results of this study suggest that transgender survivors of CSA are at increased risk of specific and cumulative forms of hate crimes and stigma-enacted violence as adults.

30 **Le Compte, Circe**

Postdoctoral Research Fellow, Psychiatry

"Differences in Cognitive Performance Between Sexual Minorities and Heterosexuals by Age and Gender in a Nationally Representative Sample of U.S. Adults Ages 18 and Older"

Background: Few studies have explored differences in cognitive performance between sexual minorities (SM) and heterosexuals by sex and age. Using a nationally representative sample of U.S. persons≥ age 18, we examined differences in attention and executive function between SM and heterosexual males and females at different ages.

Methods: We used multistage probability sampling to select participants reporting sexual orientation (SM on the 2012-2013 National Epidemiologic Survey on Alcohol and Related Conditions-III (n=35,995, ages 18-90). Previously validated self-report scales of attention and executive function were used as primary outcomes; lower scores indicated poorer cognition. Key predictors were sexual orientation controlling for gender (male and female), age (young: 18-29, middle: 30-49, and older: ≥50), race/ethnicity, and years of education. We present magnitudes of differences in cognition using scales standardized across the national sample. Complex sampling weights were incorporated.

Results: SM males had lower cognition scores than heterosexual males on attention [standardized difference (sdiff): -0.26, p<.0001)] and executive function (sdiff: -0.15, p=0.007). SM females had lower attention scores (sdiff = -0.29, p<0.001) and executive function scores (sdiff: -0.12, p=0.003). Poorer attention scores also found among young SM (young male sdiff: -0.44, young females sdiff: -0.47). Worse deficits in executive function observed for older SM males (older males sdiff: -0.25, p=0.003) but not older SM females (older female sdiff: +0.03, p=0.69).

Conclusions: Young and middle age SM men and women had small to moderately poorer attention and execution function than their heterosexual counterparts, while older SM men had poorer attention and executive function than older heterosexual men. This may be due to the impact of minority stress (stigma, prejudice, and discrimination directed to

SM), which can cause psychological distress and undermine health. Gender oppression may exacerbate minority stress among SM females, who had lower significant executive function and attention scores in each age group.

31 **Liu, Mengrui**
Postdoctoral Research Scientist, Biomedical Engineering
"Inhalable Extracellular Vesicle Delivery of IL-12 mRNA to Treat Lung Cancer and Promote Systemic Immunity"

Lung carcinoma is one of the most common cancers and has one of the lowest survival rates in the world. Cytokines such as interleukin-12 (IL-12) have demonstrated considerable potential as robust tumour suppressors. However, their applications are limited due to off-target toxicity. Here we report on a strategy involving the inhalation of IL-12 messenger RNA, encapsulated within extracellular vesicles. Inhalation and preferential uptake by cancer cells results in targeted delivery and fewer systemic side effects. The IL-12 messenger RNA generates interferon-γ production in both innate and adaptive immune-cell populations. This activation consequently incites an intense activation state in the tumour microenvironment and augments its immunogenicity. The increased immune response results in the expansion of tumour cytotoxic immune effector cells, the formation of immune memory, improved antigen presentation and tumour-specific T cell priming. The strategy is demonstrated against primary neoplastic lesions and provides profound protection against subsequent tumour rechallenge. This shows the potential for locally delivered cytokine-based immunotherapies to address orthotopic and metastatic lung tumours.

32 **Liu, Yingxiao**
Postdoctoral Research Scientist, Civil Engineering and Engineering Mechanics
"Thermo-hydro-mechanical Modeling of the Rate-dependent Freeze-thaw Cycle of Ice-rich Frozen Soils"

Ground heave and settlement caused by freeze-thaw cycles is one of the main considerations of engineering design in cold regions, but predicting such deformation over time remains a great challenge in practice due to the coupled thermal-hydro-mechanical (THM) processes involved in it.

To investigate the time-dependent deformation of the water-ice-soil system and combine multiple time-dependent processes, including hydrodynamic lag, solid viscoplasticity, and ice creeping, we derive and verify a new constitutive model where ice is treated as a second solid phase, forming a skeleton in soil and deforming continuously when loaded. The phase transition between ice and water is modeled in a kinetic way based on thermodynamic equations.

THM simulations are conducted with the finite element method on both laboratory and field samples under freeze-thaw cycles from hours to months, and numerical results show good consistency with experimental and field records at both scales. We show how temperature change can induce plastic deformation in soil samples and cause strain

localization and demonstrate that how our model can provide insights into different time-dependent processes involved and allow the separation of their effects over different stages.

33 **Loffet, Elise**
Postdoctoral Research Scientist, Biomedical Engineering
"Exploiting Morphological Diversity to Identify Regulators of Buckling Morphogenesis in the Avian Gut Development and Evolution"

Recently, the study of mechanical forces has brought new insights to the more traditionally molecular view of embryonic development. In evolutionary developmental biology, however, the focus has remained on molecular programs. Our work aims to bridge this gap, asking how evolution has acted upon genes underlying biomechanics to drive morphological variations across species. Here, we focus on looping morphogenesis of the avian small intestine, a process driven by buckling of the initially straight intestine as it elongates against the constraint of its attached mesentery. Loop morphology is highly conserved in a species, and can be mathematically predicted in several species by direct experimental measurements of physical and geometric properties.

In most amniote species, including chicken (Gallus gallus), the intestine organizes into symmetric and homogeneous undulating loops. Strikingly, we observed that in ducks (Anas platyrhynchos), this symmetry is broken by an elongated loop that does not buckle, surrounded by symmetric loops that are similar to other amniotes. By investigating this local variation, we aim to understand how changes in biomechanics can enact morphological evolution. We found that differential growth between the tube and mesentery is diminished in the long loop when compared to neighboring regions with normal buckling. We also examined regional differences in gene expression by bulk RNAseq of the mesentery, identifying approximately 140 genes that are differentially expressed between the compactly looped regions of the duck intestine and the single central loop.

Working from this list of candidate genes, future work will identify a subset of genes to be tested functionally for a role in normal buckling morphogenesis of the chick intestine, leading to the potential discovery of novel regulators of buckling mechanics in the intestine. We then further intend to explore the gene regulatory network involved in this process and how it diverges between chick and duck embryo.

34 **Lu, Chenlin**
Postdoctoral Research Scientist, Biochemistry and Molecular Biophysics
"High-resolution Protection Factor Estimation via Isotope Envelope Reconstruction from Medium-resolution HDX/MS Datasets"

The problem of designing proteins with specific structures has been partially solved with the advances in physics and/or deep learning-based methods; however, it is still challenging to design proteins with customized conformational ensemble features. Protection factors (PFs), which can be directly converted to the folding free energy (ΔG),

represent all the features of a protein's conformational ensemble. In this project, we developed a computational method to calculate PFs of proteins at near-amino acid resolution using isotope envelope reconstruction from medium-resolution hydrogen deuterium exchange/mass spectrometry (HDX/MS) datasets. It builds on top of the previously published BayesianHDX by the Sali Lab by introducing isotopic envelope fitting, a new swapping-sampling technique, and HDX/MS peptide subtraction. Benchmark tests on simulated datasets demonstrated a correlation of approximately 0.99 for small proteins (< 200 residues) and around 0.90 for medium to large proteins (300-500 residues). Our method facilitates the production of high-quality datasets for training machine learning models that predict residue-resolved PFs based on a protein's molecular features. Consequently, this enables the forward-design of proteins with customized PFs.

35 **Malik, Vikas**
Postdoctoral Research Scientist, Medicine
"Multiomics Reveal Biomolecular Shifts and ER-stress in Sleep-restricted Women Affecting NSC functions"

Adequate sleep (AS) is essential for behavioral and physiological functions, yet a third of US adults sleep less than the recommended 7-9 hours. The circadian rhythm controls tissue homeostasis, in part, through adult stem cell functions. However, little is known about the mechanistic interactions between insufficient sleep and stem cell functions. Analyzing plasma from healthy women in a randomized crossover design of 6-week periods with either AS or mildly restricted sleep (RS; 1.5 h less), we identified distinct metabolites and proteins enriched after RS. RS induced a stress-like state, highlighted by the ER-stress, heat shock, ubiquitination proteins and amino acid biosynthesis, with analysis showing a strong link between RS and altered neuronal development. Treating neural stem cells (NSCs), derived from human embryonic stem cells, with RS-enriched metabolite candidates led to an aberrant G1 cell cycle phase and impaired differentiation into neurons, astrocytes, and oligodendrocytes. This shows how even mild RS that mimics "real-life" conditions can disrupt NSC divisions and differentiation, emphasizing how sleep can shape adult stem cell regulation and neural development.

36 **Mall, Utkarsh**
Postdoctoral Research Scientist, Computer Science
"Recognizing Anything in Satellite Images"

We introduce a method to train vision-language models for remote-sensing images without using any textual annotations. Our key insight is to use co-located internet imagery taken on the ground as an intermediary for connecting remote-sensing images and language. Specifically, we train an image encoder for remote sensing images to align with the image encoder of CLIP using a large amount of paired internet and satellite images. Our unsupervised approach enables the training of a first-of-its-kind large-scale vision language model (VLM) for remote sensing images at two different resolutions. We show that these VLMs enable zero-shot, open-vocabulary image classification, retrieval, segmentation and visual question answering for satellite images. On each of these tasks,

our VLM trained without textual annotations outperforms existing VLMs trained with supervision, with gains of up to 20% for classification and 80% for segmentation.

37 **Mihali, Andra**
Postdoctoral Researcher, Psychiatry
"Effects of Hallucination Severity and Sensory Resolution on Prior Biases in Perceptual Inference of Time Intervals in Patients with schizophrenia"

Bayesian models posit that observers combine sensory evidence with prior expectations. In the psychosis literature, models of perceptual disturbances posit that hallucinations arise due to perceptual representations of the world being biased towards prior expectations. Where do these prior biases come from? We aimed to disentangle the effects of hallucination severity and sensory resolution on prior biases in the perceptual estimation of time intervals. Following our prior work in healthy controls (Duhamel, Mihali and Horga, 2023), we extended this investigation to a group including patients with schizophrenia alongside healthy controls. 79 participants (43 patients with schizophrenia and 36 healthy controls) performed an interval timing paradigm, varying in the width/variance (Wide vs Narrow) and length/mean (Medium vs Short) of the time intervals presented, for a total of three conditions: Wide-Medium, Narrow-Medium, Narrow-Short. We replicated previously observed prior biases due to length and width, in which either longer intervals (which are encoded with higher noise) or narrower distributions (which have less uncertainty) lead to decreases in the slopes (increased central tendency). We found no differences in the interval timing estimation slopes across the control and patient groups. To measure sensory resolution, participants also performed a two-interval forced-choice temporal categorization task. We found no significant differences in sensory resolution between patients and controls and no significant correlation between sensory resolution and hallucination severity. Using linear mixed-effects models including individual differences in sensory resolution and hallucination severity (as measured with the PSYRATS AHS subscale), within the patient group we found no significant effect of sensory resolution on central tendency, but a significant effect of hallucination severity: higher hallucination severity was associated with a decrease in the width effect. Consistent with our previous findings in a non-clinical group, we thus validated the effect of hallucination proneness or respectively severity on prior biases.

38 **Mukherjee, Tamalika**
Postdoctoral Research Scientist, Industrial Engineering and Operations Research
"How to Make Your Approximation Algorithm Private"

We develop a framework for efficiently transforming certain approximation algorithms into differentially-private variants, in a black-box manner. We show that such algorithms can be made differentially private without sacrificing accuracy, as long as the function has small "global sensitivity". We achieve these results by applying the "smooth sensitivity" framework developed by Nissim, Raskhodnikova, and Smith (STOC 2007). Our framework naturally applies to transform non-private FPRAS and FPTAS algorithms into pure differentially private approximation algorithms where the former case requires

an additional postprocessing step. We apply our framework in the context of sublinear-time and sublinear-space algorithms, while preserving the nature of the algorithm in meaningful ranges of the parameters.

39 **Mukherjee, Sanjay**
Associate Research Scientist, Medicine (Hematology & Oncology)
"Metastasis and Tumor-Macrophage Hybrids (TMHs): Potential Therapeutic Targets"

Metastatic cancer remains a leading cause of cancer-related mortality. During metastasis, tumor cells detach from the primary tumor site, invade distant tissues, and establish secondary tumors. While various theories have been proposed to explain metastasis, one relatively understudied but longstanding hypothesis suggests that fusion between tumor cells and leukocytes, including macrophages, generates a hybrid cell that promotes metastasis.

In several solid cancers, circulating giant cells expressing both epithelial and macrophage markers have been identified. Their presence in peripheral blood is associated with advanced disease stage, poor survival, and resistance to therapy. Additionally, cells exhibiting epithelial and macrophage characteristics, regardless of cell size, have been described and are also linked to increased metastasis and poor survival. These hybrid cells, possessing features of two distinct lineages (epithelial and macrophage), are termed tumor macrophage hybrids (TMHs).

We hypothesize that TMH cells not only seed metastasis but also exhibit resistance to standard chemotherapies. Targeting TMH cells could potentially reduce or prevent metastasis and recurrence, thereby improving survival outcomes. Since TMH cells arise from the fusion of cells from two distinct lineages, they are characterized by the presence of cell surface proteins from both lineages. Indeed, TMH cells are defined by the expression of blood lineage markers such as CD45, CD14, and CD163, along with epithelial markers such as EpCAM and cytokeratins.

To target TMH selectively with minimal off-target toxicity, we designed a recently described combinatorial targeting system known as split-chimeric antigen receptor T-cell (Split-CAR-T) therapy. In contrast to conventional CAR T cells, which express a single CAR molecule targeting a specific tumor antigen, split-CAR T cells express two separate CAR molecules, each recognizing a different component of the tumor antigen. This split-CAR design requires the presence of both tumor antigen components for CAR T cell activation, potentially reducing the risk of off-tumor toxicity. Split-CAR-T activity was evaluated against isogeneic cells that express either EPCAM or CD163 or both or none. In vitro cytotoxicity assays revealed higher activity on cells expressing both the antigens compared to single or none. We successfully generated a specific dual-targeting CAR T-cell by splitting the T-cell activation signals. We show that dual-split CAR T cells targeting EPCAM and CD163 have higher on-target (TMH cells) activity in vitro. Our findings underscore the potential of dual-split CAR T-cell therapies as an effective immunotherapeutic approach to target TMH with reduced off-tumor activity. In future,

we plan to test the persistence and efficiency of split-CAR-T in vivo using a xenograft model.

40 **Murphy, Michael**
Associate Research Scientist, Medicine (Cardiology)
"Defective Paralog Switching Causes Neonatal Heart Failure"

RPL3L (L3-Like) is a heart- and skeletal muscle-specific paralog of the ribosomal protein RPL3 (L3). During development L3 is preferentially expressed while L3-Like is induced perinatally, coinciding with a downregulation of L3 mRNA. Recessive compound nonsynonymous mutations in L3-Like were recently linked to a severe form of neonatal dilated cardiomyopathy (DCM). Inheritance of these mutations led invariably to mortality unless heart transplant was performed within 6 months of birth. Despite the observation of fibrosis and cell death of patient tissue, the biochemical mechanisms underpinning disease progression have not been elucidated. Interestingly, research by several groups have observed that Rpl3l knockout mice survive through a compensatory increase in L3 specifically, suggesting the potential for compensation in human patients.

To investigate more thoroughly each mutation, we generated stable cardiomyocyte-like AC16 human cell lines expressing L3-Like variants as well as shRNA against L3. Variant cell lines were then analyzed for subcellular distribution, translational capacity, and rRNA processing. The majority of RPL3L DCM mutations were restricted to the nucleus. Despite similar translation defects, alterations in rRNA intermediate abundances were observed for a subset of mutants versus knockdown alone. Interestingly, downregulation of L3 mRNA was impaired in Arg161Trp cells, independently of mRNA stability, leading to rescued rRNA processing and translational capacity of these cells despite non-functional L3-Like. Immunoprecipitation-mass spectrometry (IP-MS) of nuclear fractions also highlighted altered affinity of Arg161Trp L3-Like versus other variants for rRNA biogenesis factor association.

Overall, our findings suggest that the lack of compensation in human patients may be related to the existence of a subset L3-Like variants hindering the potential for L3 upregulation through their interaction with components of the L3 and ribosome biogenesis pathway.

41 **Murra, Michael**
Postdoctoral Research Scientist, Astrophysics
"The Purest Xenon on Earth for Rare Event Searches with XENONnT"

The dark matter experiment XENONnT utilizes about 8.6 tonnes of liquid xenon for the direct search of the ever elusive Weakly Interacting Massive Particles (WIMPS) and other rare event searches, employing a dual-phase Time Projection Chamber (LXe TPC).

In order to reach world-leading senstivities for the several physics channels, the target material xenon needs to be ultra-pure. Electrogentive impurities such as oxygen can

absorb or capture the created photons and electrons after a particle interaction inside the detector, diminishing the potential dark matter signals.

This poster will outline the purification techniques developed at Columbia for XENONnT to produce the purest xenon on Earth.

42 **Nishiwaki, Noriyuki**
Postdoctoral Research Scientist, Herbert Irving Comprehensive Cancer Center
"Prrx1 Regulates Acinar Cell Plasticity in Kras-driven Pancreatic Acinar-to-ductal Metaplasia"

Introduction: Acinar cells undergo de-differentiation after injury to a progenitor-like cell type with ductal characteristics termed acinar-to-ductal metaplasia (ADM). In the absence of oncogenic mutation, the ADM lesions resolve and reform the acinar compartment (we terms this as adaptive ADM). However, in the presence of oncogenic Kras mutations (we terms this as oncogenic ADM), acinar cells undergo neoplastic transformation after ADM and evolve to pancreatic intraepithelial neoplasia (PanIN), a well-known precursor of pancreatic ductal adenocarcinoma (PDAC). Herein, we explore the role of the Paired-Related Homeobox1 transcriptional factor (Prrx1) in adaptive ADM and the relationship between Prrx1 and mutant Kras in oncogenic ADM.

Methods: We generated tamoxifen-inducible Ptf1aCreERT;Rosa26YFP/YFP (abbreviated as Prrx1WT) mice and bred in the Prrx1fl/fl allele to make (abbreviated Prrx1KO) mice and subjected them to caerulein (CCK analog) induced acute pancreatitis, a well-estabished model. We created a time course for both mouse genotypes subjected to acute pancreatitis for histological analysis. Then, we performed 3D ex vivo acinar cultures of Prrx1WT and Prrx1KO mice. Additionally, we generated novel Pdx1-Cre;LSLKrasG12D/+;Prrx1fl/fl;Rosa26YFP/YFP (KCY Prrx1KO) mice, in which mutant Kras is efficiently expressed and Prrx1 is deleted in a pancreas-specific manner. KCY Prrx1WT and Prrx1KO mice were sacrificed at 3 months and 5 months for histological analysis.

Results: Immunofluorescence (IF) staining revealed that Prrx1KO mice had fewer ADM lesions compared to Prrx1WT mice at Day 3 post-caerulein. Ex vivo cultures demonstrated a substantial increase of cystic structures, which are representative of ADM in Prrx1WT cultures compared to Prrx1KO cultures. IF staining also showed that KCY Prrx1KO mice had fewer ADM lesions compared to Prrx1WT mice at at the 5 months time point.

Conclusions: Prrx1 can influence adaptive ADM formation. Moreover, Prrx1 can influence ADM formation in the presence of oncogenic Kras mutations. Our data suggest that Prrx1 facilitates PDAC progression through ADM formation.

43 **Ophaswongse, Chawin**
Postdoctoral Research Scientist, Mechanical Engineering
"Training Seated Postural Coordination in a Virtual Reality Reaching Game by Active

Pelvic Guidance from a Robotic Exoskeleton"

Individuals with neurological impairments with deficits in trunk control have difficulty maintaining and controlling upright posture during static or dynamic sitting. Passive devices may support the trunk in a wheelchair at the expense of the user's mobility, and opportunities for postural rehabilitation training are compromised as a result. This paper presents novel seated postural training using the pelvic Wheelchair Robot for Active Postural Supports (pWRAPS) to improve upper body coordination within tasks that require pelvic range of motion (ROM) performed in a Virtual Reality (VR) environment. We investigated the effects of active pelvic guidance on a subject's performance of upper body coordination while performing a continuous via-point-reaching task in four different directions. Twenty-four able-bodied young adult volunteers were assigned into three groups (eight per group). The first group (Trans/C-VF) experienced VR training with controlled visual feedback (C-VF) of moving hand target without pWRAPS actively guiding the pelvis or the transparent (Trans) mode. The second group (Traj/C-VF) had their pelvis actively guided by pWRAPS via a trajectory (Traj) while simultaneously tracking the same C-VF hand target. The third group (Traj/E-VF) had their pelvis actively guided with Error-base visual feedback (E-VF). The results support our hypotheses that the groups with active pelvic guidance adjusted their pelvic and upper body trajectories closer to the target, leading to greater improvement in task performance compared to the control group without active pWRAPS. This new training approach can potentially be adapted to postural rehabilitation for wheelchair users with limited trunk control.

44 **Osawa, Itsuki**
Postdoctoral Research Fellow, Medicine (Cardiology)
"Plasma SVEP1 Levels Predict Cardiovascular Events in Hypertrophic Cardiomyopathy Beyond Conventional Clinical Risk Models Including NT-proBNP"

Background: Hypertrophic cardiomyopathy (HCM) is the most common genetic heart disease with a prevalence between 1 in 200 to 500. HCM can lead to major adverse cardiovascular events (MACE) such as heart failure (HF) hospitalization and cardiac death. Sushi, von Willebrand factor type A, EGF and pentraxin domain containing 1 (SVEP1) is a large extracellular matrix protein that circulates in plasma. Recent studies have found that SVEP1 not only promotes inflammation and atherosclerosis but is also associated with the risk of MACE in patients with HF with reduced ejection fraction. However, it is unknown whether adding plasma SVEP1 levels to clinical predictors including NT-proBNP improves the prognostication in patients with HCM.

Hypothesis: Including plasma SVEP1 levels will improve the performance of the conventional model based on clinical predictors plus plasma NT-proBNP levels for predicting future MACE in patients with HCM.

Approach: We performed a multicenter prospective cohort study of patients with HCM. The outcome was MACE, defined as a composite of HF hospitalization or cardiac death. After dividing the cohort into four groups using the median levels of plasma SVEP1 and NT-proBNP, we compared the risk of the outcome event using the Cox proportional

hazards model adjusting for 15 clinical predictors known to be associated with MACE in HCM. We also developed a Lasso-regularized Cox proportional hazards model to predict the time to first MACE by adding SVEP1 to the 15 clinical predictors with or without NT-proBNP in the training cohort (randomly selected 75% of the cohort). We then compared the predictive performance in the test cohort (25% of the cohort) using the C-statistic of each model.

Results: During a median follow-up of 1.9 (25 percentile-75 percentile, 0.7-4.3) years, the outcome event occurred in 63 (10%) of 610 patients. The four groups stratified by the median of SVEP1 and NT-proBNP levels had different risks of the outcome event (log-rank p<0.001). Even in the groups with lower-than median NT-proBNP levels, the high-SVEP1 group had higher risks of MACE compared with the low-SVEP1 group (adjusted hazard ratio 4.52, p=0.042). In the prediction of time to first MACE, the addition of SVEP1 improved the C-statistic of the clinical model (0.88 vs. 0.77, p<0.001) and that of the clinical plus NT proBNP model (0.87 vs. 0.78, p=0.011). The clinical plus SVEP1 model also outperformed the clinical plus NT proBNP model (0.88 vs. 0.78, p=0.005).

Conclusions: In the present multicenter prospective cohort study of 610 patients with HCM, SVEP1 improved MACE risk stratification when added to the conventional model consisting of clinical predictors plus NT-proBNP. SVEP1 also exhibited a superior predictive ability than NT-proBNP to predict MACE in patients with HCM. These data collectively indicate that SVEP1 provides additional risk stratification and may be a better biomarker than NT-proBNP for the prognostication of patients with HCM.

45 **Perry-Hauser, Nicole**
Adjunct Associate Research Scientist, Psychiatry
“Adhesion GPCR Latrophilin-3 Modulation of Dopaminergic Neurotransmission”

Cell adhesion molecules, such as adhesion G protein-coupled receptor latrophilins (ADGRLs), play crucial roles in nerve terminal function. Knockout of ADGRL3 in various model organisms leads to hyperactivity and disrupted dopaminergic neurotransmission. Dopamine (DA) signaling governs fundamental processes like reward, motivation, impulsivity, and learning, with dysregulation implicated in numerous neuropsychiatric disorders. Hence, targeting ADGRL3 could offer a novel approach to modulate dopaminergic neurotransmission.

Striatal DA is associated with reinforcement learning, and DA is released in response to reward-predicting cues. Previous findings in ADGRL3 KO mice indicate increased impulsivity and motivation in behavioral tasks, but how this relates to altered DA neurotransmission is unknown. In this study, we investigated the involvement of the DA system in reward processing in ADGRL3 knockout mice using in vivo fiber photometry with the biosensor, dLight1.2. Mice were subjected to the progressive ratio schedule of reinforcement task, a standard method for assessing motivation in animals, while undergoing imaging in the nucleus accumbens. Our findings reveal that while ADGRL3 knockout mice behaved similarly to wild-type mice, their DA levels were significantly

lower, particularly when the photometry signals were aligned with lever extension and dipper up events.

46 **Piorczynski, Ted**
Postdoctoral Research Scientist, Medicine (Hematology & Oncology)
"Novel Combination Epigenetic Therapy Restores Immunogenicity in Diffuse Large B Cell Lymphoma"

Molecular studies have identified transcriptional repression leading to decreased immunogenicity as a driver in diffuse large B-cell lymphoma (DLBCL). Transcriptional activators such as belinostat and tazemetostat are approved for some types of lymphoma but have limited single agent activity in DLBCL. Dual epigenetic targeting, on the other hand, has been shown to cause potent cytotoxicity in preclinical models of DLBCL. We hypothesize that treatment with YF2, a first-in-class histone acetyltransferase activator discovered at Columbia University, in combination with belinostat or tazemetostat increases transcriptional activity and restores tumor immunogenicity in DLBCL. Cells were treated with single agents or with YF2 in combination with either belinostat (YF2+belino) or tazemetostat (YF2+taz) for six days and collected for viability, western blot, and flow cytometry analyses. To measure the effects of YF2 combination treatment in vivo, BALB/c mice were engrafted with syngeneic DLBCL cells and segregated into one of six treatment groups: control, belinostat, tazemetostat, YF2, YF2+belino, and YF2+taz. Mice were treated for a total of 21 days and tumor volumes and overall survival were recorded. Combination treatment synergistically decreased cell viability as measured by excess over Bliss (EOB) scores. Treatment with YF2+belino increased H3K27 acetylation while YF2+taz decreased methylation via western blotting, indicating transcriptional activation. Combination therapy increased markers of immunogenicity, including MHC-I, -II, and B2M, across all cell lines as measured via western blotting and flow cytometry. The epigenetic therapies were tolerated well by the mice and levels of PD-L1, an immune regulator, significantly decreased following both combination therapies. Treatment with both YF2+belino and YF2+taz led to significantly decreased tumor volumes and increased overall survival. In summary, these data propose YF2 combination treatment as a means to increase tumor immunogenicity and provide the framework to evaluate epigenetic therapy with immunotherapies as a means to target DLBCL.

47 **Qian, Jin**
Associate Research Scientist, Medicine
"A CXCR4 Partial Agonist TFF2-MSA Improves Anti-PD-1 Immunotherapy in Advanced Gastric Cancer by Targeting PMN-MDSC"

Introduction: Advanced gastric cancer poses a challenge for PD-1 immunotherapy due in part to the prevalence of polymorphonuclear myeloid-derived suppressor cells (PMN-MDSCs). PMN-MDSCs are mostly immature granulocytes but coexist with mature neutrophils, complicating their precise targeting. While PMN-MDSCs highly express CXCR4, recent clinical trials suggest that CXCR4 antagonists may provide limited additive efficacy to PD-1 blockade. This study explored the efficacy of a secreted

CXCR4 partial agonist, trefoil factor family 2 (TFF2), in the context of anti-PD-1 refractory gastric cancer.

Methods: We fused mouse TFF2 with murine serum albumin to generate a novel TFF2-MSA peptide with extended half-life, and evaluated its therapeutic effects with or without anti-PD-1 antibody. As histidine decarboxylase (HDC) is expressed in immature neutrophils, we used the HDC-GFP transgene to track PMN-MDSC in vivo. The HDC-GFP mice received subcutaneous or orthotopic implantation of murine syngeneic gastric cancer cells and subsequent treatments. Additionally, human blood was assessed for both serum TFF2 and immune profiles.

Results: The combination of TFF2-MSA plus anti-PD-1 antibody displayed remarkable synergy, boosting intratumoral cytotoxic CD8 T cells by 50-fold, leading to tumor regression or eradication, 80% reduction of distant metastasis and 2-fold extension of mouse survival. The immunosuppressive HDC-GFP+ PMN-MDSCs expressed the highest level of CXCR4 among immune cells, and TFF2-MSA treatment systematically reduced HDC-GFP+ PMN-MDSCs in the tumor, blood, spleen and their myeloid progenitors in the bone marrow. In contrast, CXCR4 antagonist AMD3100 in combination with anti-PD-1 failed to restrict tumor growth or PMN-MDSCs. Further single-cell RNA-seq and functional assays revealed that combination of TFF2-MSA plus anti-PD-1 induced a skewing of remaining tumor HDC-GFP+PMN-MDSC compositions from highly immature CD300ld+ subsets to less immature subsets expressing interferon-stimulated genes, accompanied by reduced immunosuppression and increased antigen presentation functions. Rather than local reprogramming, this compositional shift stemmed from an IRF1-driven interferon response in splenic HDC-GFP+ PMN-MDSCs. In human, PMN-MDSCs marked by LOX1 significantly expanded in the blood of gastric cancer patients compared to healthy donors. Human LOX1+ PMN-MDSCs showed an inverse correlation with T cell number, activation, proliferation and the serum TFF2 level.

Conclusions: TFF2-MSA synergizes with PD-1 blockade by selectively targeting CXCR4high PMN-MDSCs. This study provides a rational for a novel combination therapy of the CXCR4 partial agonist, TFF2-MSA, rather than CXCR4 antagonists, plus PD-1 blockade for treatment of advanced gastric cancer.

48 **Salerno, John**
Postdoctoral Research Scientist, Social Work
"A Latent Profile Analysis of Psychosocial Stressors and Buffers for PTSD Symptoms Among Latinx Immigrant Youth"

Introduction: Immigrant youth from the Northern Triangle (NT; El Salvador, Guatemala, Honduras) are a unique, vulnerable, and emerging population in the U.S. Immigrant youth from the NT face risk for stressors across the phases of migration (e.g., forced family separation), which may encourage PTSD symptoms. Yet, psychosocial buffering resources (e.g., social support) during post-migration have strong potential to prevent PTSD through mitigating the negative effects of past stressors. Therefore, understanding

the intervenable psychosocial factors associated with PTSD among NT immigrant youth is an urgent gap in the scientific literature.

Methods: Primary surveys assessing stressors across the phases of migration (pre- to post-migration victimization and family separation), immigrant-related minority stress, psychosocial buffering factors (family, peer, and school support, and ethnic identity importance), and PTSD symptoms were administered (N=172). Latent profile analysis was conducted to identify profiles that varied at the intersections of immigrant minority stress and psychosocial buffering factors. Linear regression was used to examine the associations of latent profile membership with PTSD symptoms.

Results: On average, youth were 17.6 years old and had lived in the U.S. for 2.7 years. Youth were primarily heterosexual (92%), female (63%), and born in El Salvador (76%). A three latent-profile model was identified: 1) moderate stress/low buffering (weak resources), 2) moderate stress/moderate buffering (average resources), and 3) low stress/high buffering (strong resources). Youth in the strong resources group were significantly protected from greater PTSD symptoms compared to youth in the average and weak resources groups. Post-migration victimization was significantly and positively associated with symptoms.

Conclusion: This study is among the first to reveal that NT immigrant youth may require strong psychosocial buffering resources and low immigrant-related minority stress to experience optimal mental health and PTSD prevention. Further research is warranted to address trauma and promote resilience and healing in this emerging and vulnerable population.

49 **Schafer, Matthew**
Postdoctoral Research Fellow, Psychiatry
"Common Cause Inference as a Generative Model of Delusions"

Delusions are beliefs held with high and unchanging certainty, despite contradictory evidence. Existing models of delusions based on prior-biased inferences capture formal features of delusions and have received empirical support. However, these models miss the core phenomenological features of delusions, including their common themes and structure. Delusions tend to consist of beliefs that explain the world in terms of hidden, preternatural causes in the form of complex narratives. Here, we introduce a novel framework for explaining delusions: the common cause inference model. Delusions are defined as beliefs that explain sets of unrelated observations with a common, deeply hidden cause. Such beliefs are difficult to falsify, leading to the classic delusional symptoms of high and unchanging belief certainty. Such a structure also entails inferring relationships between unrelated events, which can result in complex and bizarre associations, explaining the often implausible content of delusions. We provide a proof-of-principle demonstration that prompting a large language model (LLM) to generate a single explanation for multiple disconnected events produces explanations with similar themes and narrative structures as seen in delusions. We also outline plans to test these ideas, using naturalistic tasks and LLMs. By combining these methods with our novel

theoretical approach, we hope to advance our understanding of delusions by explaining both their structural and subjective characteristics.

50 **Shanmugam, Sri Karthika**
Postdoctoral Research Fellow, Physiology and Cellular Biophysics
"Hacking the Ubiquitin Code to Distinctively Modulate Ion Channel Functional Expression"

Ubiquitin is a powerful modulator of ion channel fate controlling varying aspects including stability, sub-cellular localization and function. The mechanistic basis and full scope of ubiquitin-mediated regulation of ion channel functional expression has remained elusive due to complexity of the ubiquitin code, with a myriad of polyubiquitin chain conformations possible, and an inability to achieve substrate-specific control of the ubiquitome. Here we developed a toolkit of engineered deubiquitinases (enDUBs) featuring a GFP-targeted nanobody fused to catalytic domains of DUBs with preferences for hydrolyzing distinctive polyubiquitin linkage types: OTUD1 - K63; OTUD4 - K48; Cezanne - K11; TRABID - K27/K33; and USP21 - non-specific. Co-expressing each of the enDUBs with YFP-tagged KCNQ1 (Q1) channels in HEK293 cells led to decreased channel ubiquitination but produced quantitative and qualitative differences in Q1 expression. NanoCezanne and nanoTRABID significantly increased Q1 surface density and ionic currents, whereas nanoOTUD1 and nanoUSP21 yielded more moderate effects. In sharp contrast, nanoOTUD4 downregulated Q1 surface density and currents. The impact on steady-state Q1 surface density was achieved by divergent mechanisms – nanoTRABID increased channel forward trafficking to the surface, while nanoOTUD4 reduced channel forward trafficking, with both having no impact on endocytosis. NanoCezanne increased forward trafficking and decreased endocytosis, while nanoOTUD1 decreased both forward trafficking and endocytosis. The E3 ligases NEDD4L and ITCH both eliminate Q1 functional expression but with different polyubiquitin signatures as assessed by mass spectrometry. NanoOTUD1, nanoCezanne and nanoUSP21 rescued Q1 channels downregulated by either NEDD4L or ITCH, whereas nanoTRABID selectively reversed the impact of ITCH but not NEDD4L. Finally, linkage-specific enDUBs displayed varying capabilities to rescue distinct trafficking-deficient mutant Q1 channels that cause long QT syndrome and predispose to sudden cardiac death. The results reveal a rich multi-faceted role of linkage-specific ubiquitination in regulating ion channel with implications for targeted therapies for devastating ion channelopathies.

51 **Shimamura, Yuko**
Postdoctoral Research Fellow, Medicine
"Decoding the Regulators of Human Organ Size in Lung Development"

Evolution changes the size of animals to adapt to the environment. Organ size regulation is a fundamental program of the developmental process, however, the molecular program that regulates more than thousands of changes in organ size remains a mystery. Exploring the organ size regulators in organogenesis programs by cross-species analyses may unlock the hidden mechanism of organ size diversification. We discovered a core organ-

size regulation program (COSRP) that is well-conserved in swine and human lungs but less so in mice using large-scale single-cell transcriptome analysis during swine lung development. Strikingly, human COSRP promoters showed a higher homology to evolutionary-distant pigs and large animals than evolutionary-close small rodents. This result indicates that the COSRP promoter region is a conserved developmental program for large lung size that correlates to organismal size. Loss-of-function studies in human iPSC-derived lung organoids confirmed that COSRP genes significantly reduced organoid size. Our cross-species analysis provides a molecular foundation of swine lung development and unveils previously unknown animal size regulation encoded in COSRP, independent of global genome-wide evolution, relevant to various fields such as evolution, development, cancer, zoology, and biotechnology.

52 **Simani, Leila**

Postdoctoral Research Scientist, Neurology/Cognitive Neuroscience

"The Effectiveness of Anodal tDCS and Cognitive Training in the Improvement of Cognitive Functions in Multiple Sclerosis"

Background: Around 40%-70% of patients with multiple sclerosis (MS) may experience cognitive impairments during the course of their disease with detrimental effects on social and occupational activities. Anodal transcranial direct current stimulation (a-tDCS) has been investigated in fatigue, cognitive and mood disorders related to MS, but to date, few studies have examined effects of tDCS with cognitive training on cognitive performance in MS. On the other hand, RehaCom is a computerized software that improves cognitive dysfunctions.

Objective: This study aims to investigate the effects of a multi-session a-tDCS protocol with and without RehaCom on cognitive performance.

Methods: Eighty MS patients were randomly assigned to a-tDCS, a-tDCS pair cognitive training, cognitive training, and sham groups for 10 daily sessions. Integrated Auditory Visual-2 (IVA-2), Rey Auditory Verbal Learning Test (RAVLT), Digit Span tasks, and Rey-Osterrieth complex figure test (ROCFT) were used to assess cognitive function at baseline, after treatment, week 4, and week 12 later.

Results: Compared to the sham condition, significant improvement in all studied cognitive functions at the immediately after the intervention. This effect also remained at the follow-up stage for some cognitive functions in the a-tDCS and a-tDCS combine RehaCom groups were observed. In the cognitive training alone group was also attention and inhibitory control improved immediately but not significantly in follow-up. However, no significant differences were observed in cognitive scores among three groups after intervention.

Conclusion: Both a-tDCS alone and a-tDCS paired with cognitive training as compared to sham appears to be a promising therapeutic option for cognitive performance in patients with MS.

53 **Sukka, Santosh Reddy**
Postdoctoral Research Scientist, Medicine
"Efferocytosis Drives a Tryptophan Metabolism Pathway in Macrophages to Promote Tissue Resolution"

The clearance of apoptotic cells (ACs) by macrophages (Mfs), known as efferocytosis, triggers resolution signaling and continuing efferocytosis. Understanding how efferocytosis activates resolution signaling by Mfs is a key goal in this area. One general mechanism involves signaling pathways activated by metabolites derived from the phagolysosomal degradation of ACs, but the full extent of these pathways remains to be discovered. Here we explore the role of tryptophan (Trp), which is converted into bioactive metabolites, including kynurenine (Kyn), by the enzyme indoleamine 2,3-dioxygenase-1 (IDO1). We initiated the study by conducting LC-MS/MS for Trp metabolites in Mfs incubated with or without ACs. We then conducted mechanistic and causation studies in human and mouse Mfs to understand the biological roles and pathways of Trp metabolism during efferocytosis. Most importantly, we tested genetic causation of key pathway molecules in vivo using three experimental models in mice, including zymosan-induced peritonitis, dexamethasone-induced thymocyte apoptosis, and atherosclerosis regression. We show that efferocytosis by mouse and human macrophages upregulates a Trp transporter, SLC36A4, in AC-containing phagolysosomes, leading to increases in cellular Trp and, via upregulation of IDO1, the Trp metabolite Kyn. Kyn, in concert with efferocytosis-induced ERK1/2 activation, upregulates chaperones that promote the nuclear transport and transcriptional activity of the aryl hydrocarbon receptor (AhR). AhR induces the pro-resolving mediators TGF-β1 and IL-10 as well as IDO1 itself (positive feedback). Kyn-activated AhR also promotes the internalization of subsequent ACs (continuing efferocytosis) via a Src/FAK/paxillin pathway. In vivo, genetic knockout (KO) of Mf-IDO1 blocks resolution in sterile peritonitis; knockout of either Mf-IDO1 or Mf-AhR blocks resolution in the Dex-thymus model; and, most importantly, inducible Mf-IDO1-KO blocks features of plaque stabilization during atherosclerosis regression. These findings reveal a new integrated metabolism program in macrophages that links efferocytosis to resolution, with possible therapeutic implications for non-resolving chronic inflammatory diseases, notably atherosclerosis.

54 **Sun, Zhixiong**
Associate Research Scientist, Psychiatry
"Elucidating the Role of SETD1A in Schizophrenia Susceptibility using Human Cell Models"

Genetic disruption of SETD1A, a lysine methyltransferase best known for its role in mediating methylation of the lysine 4 on the histone H3 protein, is robustly associated with schizophrenia (SCZ) ($p = 1x10\text{-}12$) and confers substantial risk for SCZ (odds ratio = 20). SETD1A mutations appear to increase neurodevelopmental vulnerability but the detailed mechanisms, including the genomic binding properties and targets of SETD1A in the developing human brain, as well as the cell type-specific alterations resulting from SETD1A mutations remain largely unknown. To address these questions, we generated

forebrain organoid models of the developing human cerebral cortex derived from wild type and mutant isogenic human induced pluripotent stem cells (hiPSCs) carrying SETD1A SCZ risk mutations introduced by CRISPR/Cas9 genome editing. Chromatin profiling using CUT&Tag assays combined with RNA sequencing on sorted cortical neurons led to the identification of high-confident target genes, which are significantly enriched in neuropsychiatric genetic liability. Using single-cell RNA sequencing and follow-up experimental validation, we find that SETD1A disruption leads to the changes in the expression of lineage driver genes and altered development of cortical excitatory neurons. The aberrant transcription program underlying impaired development contains molecular signatures of key regulatory factors known to modulate neurogenesis. Our ongoing experiments are investigating the morphological and functional alterations caused by SETD1A deficiency. Our study advances our understanding of SETD1A genomic binding properties, uncovers molecular and neurodevelopmental alterations due to SETD1A mutations and may facilitate efforts for therapeutic interventions

55 **Tan, Mei**

Postdoctoral Research Fellow, Psychiatry

"Neurocognitive Phenotypes in Adolescents and Young Adults Living with HIV: Does Early Education Form the Foundations of Cognitive Reserve?"

Background: Adolescents and young adults with PHIV (AYAPHIV) are at high risk for neurocognitive impairment (NCI), i.e., deficits in language, motor skills, processing speed, and executive functions, and lower educational achievement than their uninfected peers. How patterns of NCI (i.e., neurocognitive phenotypes) are related to schooling, however, is not well understood. We characterized NCI phenotypes in a sample of AYAPHIV in Thailand and Uganda and examined their educational attainment to explore the relationship between education and phenotype in two countries with high rates of PHIV.

Methods: K-means clustering was carried out across 12 neurocognitive tests (motor speed, working memory, learning, memory, attention, processing speed, executive functioning) in two samples with PHIV— 44 in Thailand (MageT = 18.27 years, SDageT = 2.91; male = 43%) and 48 in Uganda (MageU = 16.16 years, SDageU = 2.07; male = 52%)—to generate NCI phenotypes. Demographic and education factors were compared across each country's phenotypes.

Results: In each country, three NCI phenotypes were identified: one phenotype showed no NCI, and two exhibited mixed NCI across tests. In both Thailand and Uganda, mean age did not differ across phenotypes (FTh = 2.13, p = 0.13; FUg = 2.71, p = 0.08), but mean level of educational attainment did (FTh = 6.29, p = 0.00; FUg = 3.17, p = 0.05), such that phenotypes with any NCI had lower educational attainment.

Conclusion: AYAPHIV in Thailand and Uganda exhibited distinct NCI phenotypes, including clusters of individuals without any NCI. Differences in educational attainment (for reasons as yet unknown) among all of the phenotypes suggest that higher levels of education protect against NCI. Research with adults living with HIV has shown that years

of education create a “cognitive reserve” against NCI later in life. Our results indicate that this “reserve” might be observed as early as adolescence.

56 **Thomas, Aline**
Postdoctoral Research Scientist, Neurology – Taub Institute
“Inflammatory Cytokines Profiles and Cognition Among Older Adults”

Objective: Inflammation has been shown to play a major role in the development of dementia and cognitive aging in general. Studies have focused on major biomarkers of inflammation such as C-Reactive Protein (CRP), Interleukin-6 (IL-6) or Tumor Necrosis Factor-a (TNF-a). In the present study, we explored inflammatory profiles as the combination of 23 cytokine biomarkers, and their associations with cognitive decline.

Methods: We included 1,743 non-demented participants (≥65 years-old) from the 2009 cohort of Washington Heights-Inwood Community Aging Project (WHICAP). Inflammatory profiles were identified from Principal Component Analysis (PCA) on 23 blood cytokines biomarkers. Repeated cognitive assessments, performed every 18 to 24 months for up to 12.5 years, were used to assess cognitive decline in 4 cognitive domains (memory, language, executive speed, and visuospatial functions) and in global cognition.

Results: The second PCA component identified an inflammatory profile characterized by negative loadings for anti-inflammatory cytokines (e.g., IL-3, IL-4, IL-10) and positive loadings for pro-inflammatory cytokines, such as MIP-1β and TNF-a. A higher score of this component, indicating more pro-inflammatory profile, and higher levels of its key drivers (MIP-1β and TNF-a) were associated with lower baseline cognitive performances for global cognition and executive speed, after adjustment for age, sex, race/ethnicity and ApoE-ε4. No association of PCA components with cognitive decline was observed in longitudinal analysis. However, VEGF and CRP were associated with a faster decline in global cognition.

Conclusion: Among older adults, a pro-inflammatory immune profile is associated with lower baseline cognitive performances, and some individual pro-inflammatory cytokines might be associated with faster cognitive decline.

57 **Turkcan, Mehmet Kerem**
Postdoctoral Research Scientist, Electrical Engineering
“Transfer Learning for Computer Vision in Surgery Workflows”

Introduction: Automated surgical phase recognition is a key goal for developing Computer Vision (CV) algorithms, for workflow optimization and video-based assessment. However, creating large datasets for deep learning-based CV algorithms is time-consuming. Transfer learning can help solve this problem by leveraging knowledge from one task to another. We aim to use transfer learning to recognize phases in robotic ventral hernia repairs (RVHRs) by fine-tuning a pre-trained model for robotic inguinal hernia repairs (RIHRs).

Methods: In a prior study, our group trained a ResNet-50 model using 209 RIHR recordings. Videos were downsampled to 1 frame per second, then annotated into 7 surgical phases (peritoneal scoring, mesh placement, preperitoneal dissection, reduction of hernia, out of body, peritoneal closure and transitionary idle) which the model was then trained to recognize. To adapt the model for RVHRs, we fine-tuned it with 10 RVHR recordings, a 80/20 training-validation split and 5-fold cross-validation.

Results: The RIHR ResNet-50 model with a validation accuracy of 78.43% was applied to the RVHR videos, which were annotated and used as ground truth to evaluate the model's phase recognition accuracy. After 12 epochs of fine-tuning, our model achieved 62.01% accuracy (weighted F1 score of 0.60), compared to the baseline of 43.85% accuracy (weighted F1 score of 0.42) (Figure 1).

Conclusion: Transfer learning was applied for RVHR phase recognition with an accuracy of 62.01%. This approach can facilitate the creation of CV models without as significant a time commitment by research members for manual annotations.

58 **Wieszczek, Krystyna**
Postdoctoral Research Fellow, English & Comparative Literature
"Studying Reading for Empowerment"

The research project aims to expand our capacity for literature's more conscious application to mitigating social challenges as it sets out to investigate whether reading can increase one's sense of empowerment, understood as an expansion of freedom of choice and action by increasing one's authority over decisions that affect one's life. Research shows that wellbeing is influenced by various interconnected factors, including those often dictated by our choices, such as education, employment, housing, and health. Our relationships and the media, our augmented environment, have a big impact on our identity, beliefs and attitudes – and hence such life choices. Since media industries often propel insecurity, social division, consumerism and addictive behaviours and one's environment may imbed limiting beliefs and conformism, mitigating such disempowering influences is a critical step.

Empirical studies are exploring health, wellbeing and psychological effects of literature and show that literary reading can stimulate modifications in worldview, mentalising ability (Theory of Mind) and self-understanding, helping create an openness to self-alteration and personality trait modification. This may suggest literature's potential to foster also empowerment.

The project seeks to arrive at a set of five literary works of prose and five meaningful prose excerpts that may help enhance readers' perception of disempowering influences in their environment and foster empowerment to help counter their effects. It also aims to develop an interdisciplinary methodological tool to measure for such effects and test it empirically on diverse groups of disadvantaged young readers and control groups in Italy and the United States.

59 **Zadbood, Asieh**

Postdoctoral Research Scientist, Psychology

"Impaired Hippocampal Circuitry and Memory Dysfunction in Schizophrenia"

Pattern separation and pattern completion are opposing yet complementary components of mnemonic processing that heavily rely on the hippocampus. It has been shown that processing within the dentate gyrus (DG) subfield promotes pattern separation while operations within the CA3 subfield are important for pattern completion. Schizophrenia has been associated with anatomical and functional hippocampal abnormalities, including within the DG and CA3. We hypothesized that an impairment in hippocampal circuitry in individuals with first-episode schizophrenia leads to deficits in pattern separation (mnemonic discrimination) and pattern completion (recognition memory), that these deficits contribute to delusions, and that antipsychotic treatment improves circuit functioning. We measured behavioral and neural responses during the identification of new, repeated, and similar stimuli using high-resolution fMRI in 45 medication-free or minimally-treated patients with first-episode schizophrenia and 49 matched controls. We found recognition memory and pattern separation deficits in patients and a negative association between memory performance and the severity of delusions. Neural analyses revealed deficits in both univariate BOLD responses and multivariate patterns in the hippocampus during mnemonic discrimination in patients compared to controls. Importantly, by investigating the association between trial-level neural activity and behavior before and after treatment, we found that antipsychotics normalized DG activity during pattern separation and CA3 activity during pattern completion. Lastly, trial-level cortical responses during mnemonic discrimination predicted performance in patients at baseline, suggesting a compensatory role. This study provides new insight into the impact of schizophrenia and antipsychotic treatment on memory systems and uncovers systems-level contributions to pattern separation and pattern completion.

SESSION 2 | 3:30-5pm

1 **Ajala, Rasheed**
Postdoctoral Research Scientist, Lamont-Doherty Earth Observatory
"Tectonic Rifts on the Verge of Propagation"

During continental rifting, a process that initiates the formation of ocean basins, several isolated rift segments grow, link, and connect to form a mature continuous rift system. Much of the kinematics of this process is well-understood. However, knowledge gaps persist on the dynamics, mainly due to the lack of physical observations and models capturing how tectonic strain is accommodated around propagating rifts. To address some of these questions, we study three East African Rift System segments – Mweru-Wantipa, Tanganyika, and Rukwa – where recently developed seismicity catalogs show spatial earthquake clustering at the rift tips collocated with distributed faulting. We invert both compressional and shear waves from the local earthquakes for both compressional and shear wave speeds for the upper crust in the region and further analyze the seismicity for spatiotemporal patterns. Our models show high compressional-to-shear wave velocity ratios at the rift tips and earthquake swarms that indicate fluid activity. Together, these results indicate strain localization and crustal weakening ahead of the rifts supported by hydrothermal processes. For the first time, we image a snapshot of the dynamic configuration of rift segments of a rift system on the verge of lateral growth.

2 **Arad, Elad**
Postdoctoral Research Scientist, Chemical Engineering
"DNA Information-editing Tools for Reconfigurable Nanoparticle Architectures"

Biological organisms have developed comprehensive machinery for organizing matter into structures with specific functions and for reconfiguring their states in response to external signals. Unlike biology, most nanomaterials remain static, unable to adapt, change or reconfigure in response to stimulation. Transforming materials into molecular machines requires a dynamic nature with precise activation mechanisms and behavior. DNA nanotechnology methods offer a powerful means of controlling matter at the nanoscale, especially when combined with other types of nanoparticles. However, there are no methods of orchestrating reconfiguration of these complex nanostructures. Herein we aim to unravel the principles for transforming static DNA-origami into dynamic material using CRISPR-Cas technology. Controlling and editing the DNA backbone using CRISPR-Cas sequence-editing, reconfiguration of the DNA scaffold will exert control over its covalent bonds, conformation, and states. As a proof of concept, we aim to create a DNA/nanoparticle lattice with reconfigurable d-spacings. Using Cas editing we aim to achieve supramolecular asymmetry in the DNA-crystal. This goal converges biological methods and nanotechnology, achieving precise and dynamic structures while applying specific-editing tools to manipulate biopolymer system (the DNA origami).

3 **Bacon, Conor**
Postdoctoral Research Scientist, Lamont-Doherty Earth Observatory
"AVERT: An Open System for Multi-Parameter Volcano Monitoring"

The ability to effectively stream multi-parameter instrumental data from active volcanoes is a key challenge in the drive to develop the next generation of physics- and data-based eruption forecast models. Here we report on the development and field testing of a multi-parameter, real-time, open-data volcano monitoring system through our collaborative project—AVERT: Anticipating Volcanic Eruptions in Real-Time.

The AVERT system incorporates: a broad suite of traditional and novel instrumentation for volcano monitoring; power-efficient radio and satellite telemetry; and a low-power single-board computer at each site to manage data harvesting, telemetry, and preliminary in-situ analysis, enabling high-fidelity control over data bandwidth usage. The small form factor, modular design of the system enables rapid deployment and straightforward extension to a wide variety of instrumentation. The design plans and software for both remote and server-side management of the system will be openly available.

Cleveland volcano—situated in the remote Aleutian arc, Alaska—was used as the first field testbed for the system, deployed in September 2022 in partnership with the Alaska Volcano Observatory. We will present an overview of the data and some initial analyses from the broad suite of instruments, including seismic, magnetic, geodetic, imagery, gas, and weather data. A second test deployment at Poás volcano, Costa Rica, took place in November 2023, with partners from Observatorio Vulcanológico y Sismológico de Costa Rica (OVSICORI). This second deployment complements the existing instrumentation at Poás, and acted as a community platform for real-time data gathering and telemetry during a week long field workshop on the volcano held in February 2024.

4 **Batra, Nitika**
Postdoctoral Research Scientist, Electrical Engineering
"A Non-contact Fabric Drying Process Utilizing a 40 kHz Ultrasonic Transducer"

The rise in global warming is primarily caused by the emissions produced by the demand for electricity; therefore, addressing this issue requires making energy-efficient electrical appliances as one approach. One example of an energy-intensive appliance is an electric fabric dryer. The research analysis highlights the potential for enhanced efficiency in the drying cycles, with approximately 30% of the overall electricity being squandered during the drying process. This study presents a proposal for the utilization of ultrasonic technology in fabric drying operations. The objective is to decrease power consumption associated with the energy-intensive process and improve fabric quality by safeguarding it against the detrimental effects of high-temperature heating that not only reduce the life span of the fabric but also generate micro-fabrics that are harmful for the environment. Conventionally, the fabric is dried using a direct contact approach in ultrasonic drying to conserve energy. This methodology involves the direct interaction between the fabric and the vibrating ultrasonic transmitter, wherein the atomization process facilitates the extraction of water molecules from the material. The focus of this study is to explore the application of a non-contact method for the purpose of drying. Two ultrasonic transducers operating at a frequency of 40 kHz were employed to generate a high intensity standing wave field. This sound field was utilized for the drying experiment, wherein the sample was meticulously positioned at the anti-node location within the field.

The experimental procedure was replicated using various input voltages and distances between the transducers. The investigation focused on analyzing the moisture content characteristics with regard to the drying rate and duration, which resulted in the weight loss of the sample under test due to moisture removal.

5 **Bhattarai, Prabesh**
Associate Research Scientist, Taub Institute
"Rare Genetic Variation in Fibronectin 1 (FN1) Protects Against APOEε4 in Alzheimer's Disease"

The risk of developing Alzheimer's disease (AD) significantly increases in individuals carrying the APOEε4 allele. Elderly cognitively healthy individuals with APOEε4 also exist, suggesting the presence of cellular mechanisms that counteract the pathological effects of APOEε4; however, these mechanisms are unknown. We hypothesized that APOEε4 carriers without dementia might carry genetic variations that could protect them from developing APOEε4-¬-mediated AD pathology. To test this, we leveraged whole genome sequencing (WGS) data from human cohorts and identified potentially protective variants segregating exclusively among unaffected APOEε4 carriers. In homozygous unaffected carriers, we identified 510 rare coding variants. Pathway analysis of the genes harboring these variants showed significant enrichment in extracellular matrix (ECM)-related processes. We prioritized two genes: (FN1) and collagen type VI alpha 2 chain (COL6A2) that are known to be expressed at the blood-brain barrier (BBB), for postmortem validation and in vivo functional studies. The FN1 and COL6A2 protein levels were increased at the BBB in APOEε4 carriers with AD. Brain expression of cognitively unaffected homozygous APOEε4 carriers had significantly lower FN1 deposition and less reactive gliosis compared to homozygous APOEε4 carriers with AD, suggesting that FN1 might be a downstream driver of APOEε4-mediated AD-related pathology and cognitive decline. To validate our findings, we used zebrafish models with loss-of-function (LOF) mutations in fn1b – the ortholog for human FN1. We found that fibronectin LOF reduced gliosis, enhanced gliovascular remodeling and potentiated the microglial response, suggesting that pathological accumulation of FN1 could impair toxic protein clearance, which is ameliorated with FN1 LOF. Our study suggests vascular deposition of FN1 is related to the pathogenicity of APOEε4, LOF variants in FN1 may reduce APOEε4-related AD risk, providing novel clues to potential therapeutic interventions targeting the ECM to mitigate AD risk.

6 **Calvary, Lisa**
Postdoctoral Research Scientist, Biomedical Engineering
"Application of Tissue-scale Tension to Avian Epithelia in Vivo to Study Multiscale Mechanical Properties and Inter-germ Layer Coupling"

As cross-disciplinary approaches drawing from physics and mechanics have increasingly influenced our understanding of morphogenesis, the tools available to measure and perturb physical aspects of embryonic development have expanded as well. However, it remains a challenge to measure mechanical properties and apply exogenous forces on the tissue scale in vivo, particularly for epithelial tissues. Exploiting the size and accessibility

of the developing chick embryo, here we describe a simple technique to quantitatively apply exogenous forces on the order of ~1-100 μN to the endodermal epithelium. To demonstrate the utility of this approach, we performed a series of proof-of-concept experiments that revealed fundamental and unexpected mechanical behaviors in the early chick embryo, including distinct cell mechanotypes within the presumptive midgut endoderm, complex non-cell autonomous effects of actin disruption, and a high degree of mechanical coupling between the endoderm and adjacent paraxial mesoderm. Further, we extended this technique to the ectoderm, determining that forces on the order of ~10 μN are sufficient to unzip the neural tube during primary neurulation. Together, these findings provide descriptive, yet fundamental insights into the mechanical nature of the early avian embryo, and provide a useful tool for future investigations of how morphogenesis is influenced by mechanical factors.

7 **Chang, Michelle**

Postdoctoral Clinical Fellow, Medicine (Infectious Diseases)

"Predictors of Asymptomatic Sexually Transmitted Infections Among Under-Resourced Women in the Dominican Republic"

Background

Sexually transmitted infections (STIs) remain an important cause of morbidity, especially among women, and potentiate the transmission of HIV. In most resource-constrained settings, STIs are managed syndromically. Prevalent asymptomatic infections and the nonspecific nature of syndromes limit this approach. Understanding the predictors of asymptomatic STIs is crucial to improving screening and prevention strategies. We examined correlates of asymptomatic Chlamydia trachomatis (CT), Neisseria gonorrhoeae (NG), Treponema pallidum (TP), and Trichomonas vaginalis (TV) among women in the Dominican Republic (DR).

Methods

We sampled asymptomatic cisgender women from a time- and place-sampling study conducted in the DR 2015-2019 among several populations, including people with HIV (PWH), sex workers (SW), pregnant youth (PY), and residents of bateyes (RB). We defined asymptomatic as absence of self-reported vaginal discharge, dysuria, and genital lymphadenopathy, pain, and ulcers. STIs were detected through nucleic acid amplification test for urogenital, pharyngeal, and rectal CT and NG, urine TV assay, and rapid plasma reagin. We conducted descriptive analyses and examined associations between sociodemographic, clinical, and behavioral factors and presence of STI using logistic regression analyses.

Results

Among 939 asymptomatic women, 238 were PWH, 267 SW, 315 PY, and 119 RB. Mean age was 29 years. Of the 223 with STI, 193 had one infection. There were 134 cases of CT, 35 of NG, 49 of TV, and 36 of TP. STI prevalence was 45.3%, 31.8%, 11.7%, and 11.2% in PY, SW, RB, and PWH, respectively. In the adjusted analysis, age ≤24 (aOR 2.17, 95% CI 1.45-3.29) and age ≤14 at sexual debut (aOR 1.62, 95% CI 1.11-2.37) were associated with asymptomatic STI.

Conclusions
Younger women and women reporting early sexual debut may benefit from targeted asymptomatic screening for STIs and prioritization for STI prevention interventions in resource-constrained settings where syndromic management is the standard of care.

8 **Chowdhury, Srikanta**
Postdoctoral Research Fellow, Medicine (Preventive Medicine)
"Peptidergic Cells Expressing CCK in the Brainstem Regulate Satiation"

Termination of an ongoing meal occurs either through satiation (Lt. satis meaning "enough") or anorexic cues originating internally (malaise) and externally (threat). While the role of brainstem nuclei, such as the parabrachial nucleus, in conveying anorexigenic signals to the forebrain has been studied extensively, the fundamental mechanisms through which the mammalian brain regulates satiation remain unknown. Using spatially resolved molecular phenotyping at both transcriptional and translational levels, we identified a previously uncharacterized neuronal population within the brainstem's dorsal raphe nucleus (DRN) that governs satiation. This particular DRN neural population produces the peptide hormone cholecystokinin (CCK) and other neuropeptides, but interestingly, it does not seem to generate markers for classical, fast neurotransmitters. Activated upon re-feeding, these CCK populations selectively influence food intake by reducing meal sizes without impacting the number of meals and inter-meal intervals. This phenomenon is the hallmark of satiation. Remarkably, these neurons in the DRN can integrate various signals responsible for regulating a meal's size. These signals include thoughts about food (and their sensory representation), the sensation of food in the stomach, and signals originating from the gastrointestinal tract. This multi-level integration ability makes the CCK population an ideal candidate for a "satiation center" through which it might act to regulate short- and long-term food intake. Polysynaptic tracing studies further link these phenomena to gut-brain neuraxis, where vagal afferents facilitate gastrointestinal tracking of nutrient influx. In summary, our findings propose an obligate peptidergic brainstem population that monitors ingestion and uses this information to regulate satiation.

9 **WITHDREW**

10 **Dar, Khalid**
Postdoctoral Research Scientist, Medicine (Cardiology)
"Mammalian Cardiomyocyte Binucleation Regulates Cell Size"

In the early postnatal phase, mammalian cardiomyocytes become polyploid and binucleated/multinucleated, avoiding hyperplasia (cell proliferation) in lieu of hypertrophy (cell enlargement). It is thought that polyploidy, which results in excess DNA, causes mammalian hearts to lose their capacity for regeneration. Why does evolution generated mammalian heart with extra DNA while compromising its regenerative capacity? What is the role of extra DNA in polyploid cardiomyocytes? To answer these evolutionary questions, our lab hypothesized that preventing the cell cycle

that leads to binucleation could arrest cells in a mononucleated state. Such a mouse model could help provide insights about the evolutionary design of the mammalian heart, especially the role of polyploidy – which remains enigmatic. We generated cardiomyocyte specific p21-overexpression mice (Myh6-MerCreMer;LSL-p21) that have 70-80% mononuclear myocytes in the adult heart (compared to <20% in controls) when p21 is induced at birth. This model was tested along functional (echocardiography), structural (electron microscopy), physical (treadmill exercise) electrophysiological (Ionoptix) and proteomics (mass spectrometry) parameters. Our principal discovery is that genetically-forced mononucleation of cardiomyocytes leads to cardiac dysfunction with aging. To determine the mechanism, we performed a battery of assays. We found no significant differences in how wells cells contract between the two groups; no differences in calcium handling; no differences in metabolomics profiling; no differences in exercise capacity. Rather, our model suggests that binucleation is important for cell size enlargement. Our ongoing experiments seek to elucidate how the nucleation state regulates hypertrophy pathways in the heart in order to provide molecular insights about size control in mono- versus binucleated (or polyploid) cardiomyocytes.

11 **Darko-Boateng, Arden**
Postdoctoral Research Scientist, Physiology and Cellular Biophysics
"NEDD4-2 Recruitment to Diverse Ion Channels with Divalent Nanobodies Inhibits their Functional Expression"

Targeted recruitment of E3 ubiquitin ligases to degrade traditionally undruggable proteins is a disruptive paradigm for developing new therapeutics. A salient limitation is that <2% of the ~600 E3 ligases in the human genome have been exploited to produce proteolysis-targeting chimeras (PROTACs). NEDD4-1 and NEDD4-2 are prototypes of the 28-member HECT (homologous to E6AP C-terminus) family of E3 ligases with widespread roles in cell/developmental biology and diverse diseases including various cancers, immunological and neurological disorders, and chronic pain. The efficacy of HECT E3 ligases for PROTACs has been unexplored and is uncertain due to their complex regulation by layered intra-molecular and post-translational mechanisms. Here, we identified a nanobody that binds with high affinity to the N-lobe of the NEDD4-2 HECT domain at a site physically removed from the E2 binding site and the catalytic cysteine, as determined by cryogenic electron microscopy. Recruiting endogenous NEDD4-2 to diverse ion channel proteins -- CaV2.2, KCNQ1, ENaC -- using a divalent (DiVa) nanobody format strongly reduced their functional expression with minimal off-target effects as assessed by global proteomics, compared to simple NEDD4-2 over-expression. The results establish the utility of a HECT E3 ligase for PROTACs development; validate a class of complex multi-subunit membrane proteins as susceptible to this modality; and introduce DiVa nanobodies as a general method to generate novel genetically-encoded ion channel inhibitors.

12 **Deol, Rajinder**
Postdoctoral Research Scientist, Electrical Engineering
"A Low-cost Self-powered Sensor-network System for Renewable Gas Transportation Infrastructure System Powered Using Energy Harvesting"

Hydrogen is one of the most important fuels for a sustainable and renewable energy economy. One of the challenges with working with hydrogen, however, is that it requires the use of well-sealed pipelines due to its very fast di?usivity, flammability, and chemical reactivity leading to complication during incorporation of sensors in the delivery and distribution network. There is also a huge interest in examining the blending of hydrogen with natural gas, in which the hydrogen concentration is controlled to stay below 20 % to prevent embrittlement of the metal components commonly used in natural gas containment and transportation networks. Incorporation of sensors is especially important for these hydrogen supply infrastructures. It has been shown that a number of contaminants in the hydrogen supply can be especially harmful for fuel cell applications. In particular, epoxies commonly used in building components such as assembling fuel systems, sensors, and pipelines can foul fuel cell membranes and lead to a dramatic loss in energy delivery and irreversible damage to the fuel cell systems. Our proposed design will use a mechanical energy harvesting approach which will stimulate a high-quality factor (Q) resonator on the inside of the pipe without the need to penetrate the walls of the pipe system. Such sensors could also report on the pressure in hydrogen fuel pipelines, measure flow, and monitor the blending ratio in natural gas/hydrogen mixed delivery systems. Acoustic communication is also used to transmit information between the sensing and communication base unit, eliminating the need for pipe penetrations and risk of leaks, embrittlement, etc. Meanwhile, the sensor package will be powered with piezoelectric, solar, and flow of gas as wind energy harvesting systems. Piezoelectric energy harvesting using materials like PVDF and KNN (Potassium Sodium Niobate) was performed on a stainless-steel sheet through mechanical vibrations of a speaker. The resonance frequency that the PVDF sheet vibrates most readily and e?ciently was successfully analyzed and recorded through multiple isolation techniques. In order to observe the resonance frequency, five di?erent methods were implemented into the experiment to reduce noise. Visually, the resonance frequency can be seen from 180 Hz to 220 Hz. The experimental results confirm the visual resonance frequency and reveals external factors that can a?ect the resonance of the piezoelectric material. We were able to transmit and receive signals through the metallic pipeline at 200 kHz to 500 kHz using PVDF sensors for communication purposes. The power received through 4 mm thick solid iron pipe was 5 %, which is enough to transmit bytes of sensor data from inside the metallic pipe that acts as a Faraday cage. Meanwhile, our lab scale prototype for the energy harvesting systems generated about: 0.02 W for piezoelectric, 2 W for solar, and 0.8 W for wind. A large industrial scale version will be more economically viable.

13 **Diaz-Faes, Diego**

Postdoctoral Research Scientist, Epidemiology

“Do Executive Function and Self-esteem Play a Role in the Cycle of Violence? A Prospective Examination of the Relationship Between Childhood Maltreatment and IPV Perpetration”

Background: Existing research indicates childhood maltreatment's association with increased risk of violence in later life, including intimate partner violence (IPV), along with potential links to poorer executive function and self-esteem. However, prospective

longitudinal studies exploring the interplay of these factors are lacking. Methods: To address this gap, this study relies on a prospective cohort design involving individuals with court-sustained cases of child abuse and neglect cases (ages 0-11 years) from a Midwest metropolitan county (1967-1971) alongside demographically matched controls. Participants who experienced childhood maltreatment and their matched controls underwent follow-up assessments across multiple waves during their young and middle adulthood. Inhibition and cognitive control were evaluated at a mean age of 39, and cognitive flexibility and nonverbal reasoning were measured at a mean age of 41. Self-esteem was also assessed at a mean age of 41. Physical IPV perpetration at age 47 was evaluated utilizing two distinct scoring strategies to mitigate score skewness. Analyses were controlled for sex, age, race/ethnicity, and education. Results: Childhood maltreatment predicted lower executive function and self-esteem, both of which independently predicted IPV perpetration. Lower executive function and self-esteem mediated the relationship between childhood maltreatment and IPV perpetration in midlife irrespective of the scoring method. Conclusion: This new evidence suggests that executive functioning and self-esteem play a role in the cycle of violence, suggesting avenues for intervention and the need for further research.

14 **Dorrity, Tyler**
Postdoctoral Research Fellow, Microbiology and Immunology
"ADAR1 Regulates Endogenous dsRNA Levels in Neurons and Prevents Neuroinflammation"

Loss of RNA homeostasis underlies many neurodegenerative diseases, but the molecular mechanisms that render the brain so sensitive to perturbations in RNA remain unclear. Here I demonstrate that neurons carry an exceptionally high double-stranded RNA (dsRNA) burden. In healthy neurons, this endogenous dsRNA is immunostimulatory and is able to induce low levels of inflammation via the machinery that normally senses viral dsRNA. I report that neurons have intrinsically high levels of dsRNA due to the inherent neuronal ability to lengthen 3` untranslated regions (3`UTRs). Through the expression of the neuronal-enriched ELAVL RNA-binding protein family (ELAVL2, ELAVL3, ELAVL4), neurons lengthen 3`UTRs and increase dsRNA levels. Loss of ADAR1, a key dsRNA regulator, models the neuroinflammatory disease Aicardi-Goutières syndrome (AGS). In ADAR1 deficient neurons, dsRNA burden increases dramatically and induces toxic inflammation, ultimately inducing neuronal death via sustained activation of the dsRNA sensor PKR. Critically, depletion of ELAVL2 in ADAR1 KO neurons lead to a decrease in immunostimulatory dsRNA levels and prolonged neuronal survival. Overall, neurons are a unique cell type that constantly sense "self" dsRNA, but maintaining RNA homeostasis is critical to prevent pathology.

15 **Dsouza, Nishita**
Postdoctoral Research Fellow, Social Work
"Housing & the HEALing Communities Study: Qualitative System Dynamics for Participatory Action Research to Lessen Overdose Risk Among People Affected by Homelessness"

An estimated 11.4 million people in the U.S. experience housing insecurity, or the inability to afford or maintain residence in a safe and quality place to live. Of those, an estimated 50-70% are affected by substance use disorders (SUD) and 70-80% affected by mental illness or post-traumatic stress. The HEALing Communities Study (HCS) is a large multisite trial with the goal of overdose risk reduction through implementation of evidence-based interventions. While many implemented strategies, such as medication-assisted treatment and naloxone distribution, successfully and sustainably operate in HCS counties, key stakeholders report that housing insecurity and homelessness are significant barriers to overdose risk reduction. The aim of this study was to engage in qualitative system dynamic (SD) models to inform community-driven approaches to housing solutions for individuals with co-occurring substance use and mental illness in two HCS counties in upstate New York. Models were created using the System Dynamics Bot, a computer program leveraging a large language model to automate the creation of causal loop diagrams (CLDs) from select qualitative data (e.g., key stakeholder interviews, meeting minutes, professional presentations, and grey literature). After recalibration, the SD Bot was able to identify interdependencies and feedback structures underlying the syndemic of homelessness, substance use, and mental illness in communities. Preliminary analysis of the AI-generated CLDs has identified interconnectedness of various actors (social service decisionmakers, service providers, regional abatement task force members) and factors (housing affordability and quality, shelter restrictions) affecting overdose risk. As the development and testing of an HCS Artificial intelligence platform progresses, participatory modeling can inform future community-driven approaches to reduce overdose risk. Systems science methods hold much potential for cross-sector collaboration to improve livability and health equity among those affected by homelessness.

16 **Duarte-Cordon, Camilo**
Postdoctoral Research Scientist, Mechanical Engineering
"A Computational Viscoelastic Model of the Macaque Rhesus Cervix to Quantify Cervical Remodeling"

The cervix is a viscoelastic soft biological tissue that plays an essential mechanical function during pregnancy. To prepare for parturition, the cervix remodels, transforming from a stiff and closed structure that keeps the growing fetus in the uterus to a soft and extensible structure capable of dilating and effacing considerably under the influence of uterine contractions to allow birth at term. This process, known as cervical remodeling, is facilitated by alterations in the cervical extracellular matrix (ECM), which is composed mainly of a 3D network of collagen, glycosaminoglycans (GAGs), and interstitial fluid. Structural changes in the ECM are responsible for the anisotropic and complex equilibrium and time-dependent mechanical properties of the cervix. Computational material models of the cervical ECM calibrated with ex vivo mechanical testing data from animal and human cervical tissue have proven to be valuable tools for objectively studying cervical remodeling regarding changes in mechanical properties during gestation. However, most studies have focused on the mechanical properties of the cervix under equilibrium conditions. In a few studies examining the time-dependent response of cervical tissue, its viscoelastic properties were obtained only under compressive loading

and at two gestational points (pregnant and non-pregnant). Since the cervix exhibits a tension–compression asymmetric mechanical response, quantifying the nonlinear time-dependent properties of the cervix under tensile loading will help us better understand remodeling, particularly the role of the collagen network. Additionally, pregnancy is a protected environment; therefore, studying the relaxation response of cervical tissue from homologous human species, such as rhesus macaques, allows us to study cervical viscoelasticity at multiple and relevant gestational time points. Building on previous constitutive models, in this study, we implemented a nonlinear anisotropic viscoelastic model of the cervical ECM, which captures its force relaxation response under tensile deformation. To calibrate our model, we used force-displacement experimental data from uniaxial tension tests in cervix samples from rhesus macaques, chosen because of their homology to humans, and collected at four relevant gestational time points. This work provides insights into normal cervical remodeling, which is crucial for developing diagnostic methods and treatments for conditions such as cervical insufficiency, which is known to lead to preterm birth (birth before 37 weeks).

17 **Fantuzzi, Fabio**
Postdoctoral Research Fellow, Germanic Languages
“The Marie Skłodowska-Curie project "POYESIS": The figure of Norman Raeben”

The present paper illustrates the results of the EU-funded Marie Skłodowska-Curie project "POYESIS," a joint postdoctoral fellowship between Ca' Foscari University and Columbia University that aims to study the work and influence of artist Norman Raeben. Despite his interactions with significant exponents of the Ashcan School and the postimpressionist and modernist movements and his influence on several leading artists - such as Stella Adler, Isador Steinberg, Bill Cunningham, and Bob Dylan, to name but a few - Norman Raeben's works and teachings have yet to be studied comprehensively. The last son of Sholem Aleichem, a talented painter, and an influential mentor, his figure and impact can tell us more about the evolution of Yiddish culture and art in the 20th century in New York.

The project will provide the first catalog of his works and an edition of his papers and lectures. It will also organize the first retrospective exhibition of his works and an international conference, which will open at the Jewish Museum in Venice on November 3, 2024.

After offering an overview of the research results, the paper will highlight the main characteristics of his works and ideas and describe the creative writing technique that Bob Dylan created based on Raeben's artistic method, producing some of his most acclaimed albums ("Blood on the Tracks," "Desire," and "Street Legal") and the film "Renaldo and Clara."

18 **Fernandez Valledor, Andrea**
Associate Research Scientist, Medicine (Cardiology)
“Correlation Between Donor-Specific Antibodies and Molecular Microscope Results in Heart Transplant Recipients”

Purpose: Diagnosing antibody-mediated rejection (AMR) in heart transplant (HT) recipients remains challenging, and is based on the combination of symptoms, the existence of donor specific antibodies (DSA) and histological assessment. The Molecular Microscope (MMDx), which employs tissue-based gene expression analysis, may add important adjunctive information.

Methods: All HT recipients who had for-cause biopsy with MMDx between November 2022 - August 2023 were included. Histology results were considered positive if ISHLT >1R/1A or pAMR>0 whereas MMDx results were considered positive if definite or borderline rejection or significant parenchymal injury was present. MMDx gene-related transcripts and DSA status (class I, II and non-HLA antibodies) were recorded. Two groups were defined according to the presence of absence of DSA.

Result: 168 MMDx samples from 123 patients were included. Of those, 96 samples (57%) were associated with positive DSA. Median age was 54 years, 35% were female and 48% from White ethnicity. The median time from transplant to MMDx was longer in the DSA group in comparison with the non-DSA (28 months [IQR 16, 109; p<0.001]). There were no differences between groups in demographic characteristics. However, patients with positive DSA had higher rates of prior treated cellular (68% vs 49%; p=0.02) and ABMR (37% vs. 4%; p<0.001). Positive cell-free DNA (≥0.12%) rates were similar across the groups (p=0.75). In patients with DSA, MMDx identified ABMR twice as frequently as conventional histology (28% vs 14%; p=0.06). When stratified according to MMDx results, patients with DSA had 10 times more chances of ABMR diagnosis compared to those without DSA (28% vs 2.8%; p<0.001; Figure 1a). Regarding gene-transcripts, all the four related with ABMR were significantly elevated in the DSA group (p<0.05 for all).

Conclusion: In our cohort, patients with DSA exhibited a two-fold increase in ABMR diagnosis based on MMDx compared to histology and a ten-fold higher likelihood of ABMR diagnosis compared to those without DSA when assessed by MMDx.

19 **Floris, Elena**
Postdoctoral Research Scientist, Surgery
"Secretory Phospholipase A2 type IIA is Elevated in the Bronchoalveolar Lavage of Lung Transplant Recipients with Bile Acid Aspiration and Airway Infections"

Purpose: Inflammatory lung diseases are associated with increased airway levels of secretory phospholipase A2 type IIA (sPLA2-IIA), an enzyme that hydrolyzes phospholipids releasing arachidonic acid metabolites. Bile acids (BA) aspiration in lung transplant recipients (LTRs) predict chronic lung allograft dysfunction. Moreover, in experimental lung models BA increased sPLA2-IIA expression. We sought to investigate the relationship between aspirated BA and sPLA2-IIA in the airways of LTRs.

Methods: Prospective bronchoalveolar lavage (BAL) was obtained from 137 LTRs during surveillance bronchoscopies at 3 months post-transplant. BAL were assayed for:

conjugated and unconjugated BA by tandem mass spectrometry; inflammatory mediators by 48-multiplex; and sPLA2-IIA by ELISA. BAL microbiology was monitored. Non-parametric statistical analysis was performed.

Results: sPLA2-IIA was quantifiable in 76% of BAL samples, median concentration 376.6 pg/ml (25th-75th percentile range: 37.69-1760). sPLA2-IIA correlated with total BA levels (Spearman r=0.3331, p<0.0001). Correlation was stronger with conjugated versus unconjugated BA (r=0.3408, p<0.0001 vs r=0.2511, p=0.0031). High levels (upper tertile) of BA associated with high levels of sPLA2-IIA (X2=5.802, Fisher p=0.0204). Samples with high BA showed greater sPLA2-IIA levels, median: 955.7 pg/ml (255.3-3156) vs 217.3 pg/ml (15.65-1146) (p=0.0002). In BAL positive for bacteria the sPLA2-IIA median 642.6 pg/ml (130-3227) was greater than in samples negative for bacteria median 223.5 pg/ml (15.65-1151) (p=0.0036).
The sPLA2-IIA and BA correlation persisted in samples negative for bacteria (r=0.3199, p=0.0025). sPLA2-IIA correlated with 36/48 of the inflammatory mediators (p<0.05).

Conclusions: BAL sPLA2-IIA levels in LTRs were comparable to other inflammatory lung disorders, and markedly greater than in healthy controls (39 pg/ml). sPLA2-IIA in LTRs BAL independently correlated with aspirated BA, and associated with bacterial infections. These findings explore for the first time the role of sPLA2-IIA in lung transplantation and suggest that BAL sPLA2-IIA may serve as a marker of noxious lung allograft events as aspiration and infection.

Authors: Elena Floris, Chiara Camillo, Luke Benvenuto, Anna Miller, Frank D'Ovidio

20 **García Ruiz, Irene**
Postdoctoral Research Fellow, Ecology, Evolution, and Environmental Biology
"Fitness Drivers of Division of Labor in Vertebrates"

The division of labor among entities within a group has played a crucial role in the major evolutionary transitions, such as the shift from prokaryotes to eukaryotes and from unicellular to multicellular organisms. Attempts to explain division of labor within animal societies have focused primarily on species like eusocial insects that live in groups of highly related individuals that cooperate to gain joint fitness benefits. Yet, division of labor is also relevant in groups of individuals with lower levels of relatedness, such as those on our own species. Here we show that direct fitness benefits can select for division of labor in groups of low or unrelated individuals where selection acts more directly at the individual level. We also find that increasingly harsh environments more strongly promote division of labor, as it is predicted in early human societies.

21 **Gutierrez-Bayona, Natalia**
Postdoctoral Research Scientist, Center for Radiological Research
"Extending the Erythema Action Spectrum to Include the Far-UVC"

Guidance on UV exposure limits is vital for public health safety as it aims to minimize harmful effects while allowing for beneficial exposure. National and international

organizations, such as The American Conference of Governmental Industrial Hygienists (ACGIH), play crucial roles in the establishments of these guidelines. They consider the risk of acute effects (e.g., erythema) and long-term effects (e.g., skin cancer) in determining exposure limits, termed Threshold Limit Values (TLVs). TLVs specify the dose a person can safely receive during an 8-hour workday and 40-hour workweek without skin or eye injuries. This determination relies on action spectra which is a method used to quantify the effectiveness of each wavelength at eliciting specific biological effects. In response to the growing interest in using far-UVC (200-235 nm) radiation for controlling the spread of airborne pathogens, recent arguments have emerged for revisiting exposure limits for wavelengths below 250 nm after the thresholds set for 222 nm and 207 nm were demonstrated to be overly conservative. In response to this, ACGIH acted in 2022 and increased the TLVs for wavelengths below 240 nm. While there is much evidence suggesting that these new threshold limits are safe, the standard erythema action spectra have not been extended below 240 nm. This study assists in expanding the erythema action spectrum to far-UVC wavelengths using hairless albino mice model by reporting new skin threshold doses from 200 to 270 nm using narrow bandwidth exposures in 5 nm increments.

22 **Jerabek, Stepan**
Postdoctoral Research Scientist, Pediatrics
"Base Editing in Human Embryos Enables the Knockdown of PCSK9 without Detrimental Chromosomal Changes"

Nearly all diseases have a genetic component, and the genome received at conception is thus key to human health. Gaining greater insight into the mechanisms involved in protecting the genome following DNA damage in early human embryos will be important for understanding the origin of de novo mutations and future efforts to prevent genetic diseases. Genome editing tools enable us to introduce a specific lesion at a desired genomic location and assess the results of DNA repair. Prior research in our laboratory has revealed that CRISPR/Cas9-induced DNA double-strand breaks (DSBs) at the EYS locus lead to frequent chromosomal abnormalities in human embryos. Here, we detected segmental aneuploidies following CRISPR/Cas9 cleavage at other genes (MYBPC3, CCR5, HBG), broadening the risks of on-target DSBs in human embryos using this technology. Newer genome editing tools, such as base editing and prime editing, introduce nicks rather than DSBs. We focused on base editing of PCSK9 and injected the editing tool into human zygotes, either as RNA or purified protein. Sequencing analysis of DNA from single blastomeres revealed on-target editing efficiency of around 70%, with only one percent of indels and even fewer undesired editing byproducts. Using single nucleotide polymorphism arrays, we demonstrated that base editing does not cause segmental chromosome changes detrimental to further development. Mapped chromosomal breakages outside the targeted locus did not overlap with predicted off-target sites. To further assess potential off-target events, we derived embryonic stem cell lines from base-edited blastocyst-stage embryos. We also delivered the base editor into MII oocytes during intracytoplasmic sperm injection to determine the kinetics of base editing and the prevalence of genetic mosaicism. Overall, this work establishes new understandings of DNA repair in the early human embryo, emphasizes the risks and

potential of germline genome editing, and shapes future discussions on germline gene therapy.

23 **Jorem, Jacob**
Postdoctoral Research Fellow, Psychiatry
"Impact of Introducing a Capacity-Based Mental Health Law: A Qualitative Exploration of Stakeholder Perspectives"

Background: Decision-making capacity (DMC) is a key criterion in capacity-based health laws. Lack of DMC was introduced as a criterion for involuntary admission and treatment following amendments to the Norwegian Mental Health Care Act in 2017 to strengthen patient autonomy and reduce involuntary care. Health registry data reveal an initial reduction, followed by a return to gradual rising involuntary care rates along the pre-2017 trajectory.

Aims: To explore the possible impact of introducing a capacity-based mental health law governing involuntary admission and treatment.

Methods: Semi-structured interviews were conducted in 2018 with 60 stakeholders, 26 of which participated in follow-up interviews in 2022–23. The transcribed interviews were analysed using manifest and latent forms of thematic analysis.

Results: Participants shared similar experiences in 2018 and 2022–23, and four themes emerged: 1) increased awareness of patient autonomy and improved patient involvement; 2) altered thresholds for admission and discharge and more challenging to help certain patient groups; 3) more responsibility for primary health services; and 4) increased responsibility for family but unchanged involvement by health services.

Conclusion: Introducing a capacity-based mental health law appears to have raised awareness of patient autonomy without a corresponding emphasis on voluntary care. Post-2017 changes, including rising involuntary care rates, more severely ill patients, and increased pressure on primary health services and families, may be influenced by several factors, such as implementation of DMC, legal interpretations, reduced inpatient bed availability, and societal developments. Further research is needed to better understand these changes, possible causes, and mediating factors.

24 **Karaahmet, Berke**
Postdoctoral Research Scientist, Neurology
"Spatial Transcriptomics Analysis Identifies Glial Signatures Spatially Associated with Neuritic Plaques in Human Post-Mortem Brains"

Glial cells exhibit distinct transcriptional responses to β-amyloid pathology in Alzheimer's disease (AD). While sophisticated single-cell based methods have revealed heterogeneous glial subpopulations in the human AD brain, the histological localization of these multicellular responses to AD pathology has not been fully characterized due to the loss of spatial information. Here, we combined spatial transcriptomics (ST) with

immunohistochemistry to explore the molecular mechanisms in the neuritic plaque niche. 32 sections from the prefrontal cortices of 15 AD and 2 control cases were applied to ST arrays with spatially barcoded probes (spots) of 55μm diameter. Amyloid plaques were stained with Thioflavin S (ThioS) and astrocytes were stained using GFAP in the same ST tissue section. The immunohistochemistry data were then projected onto the ST profiles. To reconstruct the neuronal layer structure, we clustered the spots using spatially-aware algorithms. We detected 263 ThioS+ amyloid plaques, and gene expression in spots within 150μm of plaques were compared to that of distant spots (≥500μm), adjusted for cortical layer and donor. This approach identified 182 plaque-associated genes and confirmed genes previously reported in mice, such as GFAP, CLU, MBP and MOBP. Interestingly, the AD-related gene SERPINA3 was found to be upregulated at neuritic plaques. SERPINA3 is a marker of an inflammatory astrocyte subpopulation, resembling previously discovered disease-associated astrocytes in mice. Indeed, computationally deconvoluting this astrocyte subpopulation from the ST data confirmed its enrichment at plaques. Further, we found a downregulation of metallothioneins, expressed by astrocytes, indicating a potential dysfunction of metal ion homeostasis. We validate these results using immunohistochemistry and in situ hybridization. Overall, we demonstrate the heterogeneity in glial communities within the amyloid plaque microenvironment. We show evidence suggesting a spatial enrichment of SERPINA3+ astrocytes at neuritic plaques. Furthermore, the identification of the 182 plaque-proximal genes suggests involvement of processes related to inflammation, and ion transport and homeostasis. The role of these subtypes and molecular signatures in AD pathophysiology remains to be elucidated.

25 **Kizildag, Eren**
Distinguished Postdoctoral Research Scientist, Statistics
"Statistical-Computational Tradeoffs in Random Optimization Problems"

Optimization problems with random objective functions are central in computer science, probability, and modern data science. Despite their ubiquity, finding efficient algorithms for solving these problems remains a major challenge. Interestingly, many random optimization problems share a common feature, dubbed as a statistical-computational gap: while the optimal value can be pinpointed non-constructively (through, e.g., probabilistic/information-theoretic tools), all known polynomial-time algorithms find strictly sub-optimal solutions. That is, an optimal solution can only be found through brute force search which is computationally expensive.

In this talk, I will discuss an emerging theoretical framework for understanding the fundamental computational limits of random optimization problems, based on the Overlap Gap Property (OGP). This is an intricate geometrical property that achieves sharp algorithmic lower bounds against the best known polynomial-time algorithms for a wide range of random optimization problems. I will focus on two models to demonstrate the power of the OGP framework: (a) the symmetric binary perceptron, a random constraint satisfaction problem and a simple neural network classifying/storing random patterns, widely studied in computer science, probability, and statistics communities, and (b) the random number partitioning problem as well as its planted counterpart, a classical

worst-case NP-hard problem whose average-case variant is closely related to the design of randomized controlled trials. In addition to yielding sharp algorithmic lower bounds, our techniques also give rise to new toolkits for the study of statistical-computational tradeoffs in other models, including the online setting.

26 **Koukras, Alexandros**
Postdoctoral Research Scientist, Astrophysics
"Elemental Abundance Variations Across Coronal Hole Boundaries"

The fast solar wind originates from regions of open magnetic field in the Sun, which are called coronal holes; but the origin of the slow solar wind is still not well understood. The in-situ measured elemental abundances of the slow solar wind suggest that it originates from initially closed field lines. Consequently, several theories propose that the boundaries of coronal holes are the source region of the slow solar wind. Magnetic reconnection of quite sun loops with the open field lines at the boundaries of coronal holes could also explain the apparent rigid rotation of coronal holes.

Our aim is to quantify the relative abundances of different elements at the boundaries of coronal holes. Reconnection is expected to modulate these abundances through the First Ionization Potential (FIP) effect. We measure the FIP effect across coronal hole boundaries as a function of latitude on the leading and trailing edges and quantify any difference.

For our analysis we use spectroscopic data from EIS on Hinode. The wide wavelength range that it covers makes it suitable for FIP effect diagnostics. Our methodology for the FIP analysis accounts for the temperature structure of the observed region. To accomplish that we compute the differential emission measure (DEM), based on the observed line intensities of low FIP elements like iron and silicon. We then use that DEM to predict the intensity of lines from other elements, such as sulfur. Comparing the modeled to observed intensities allows us to infer the FIP bias between the coronal and photospheric abundances. Then by examining the FIP bias as a function of longitude we can determine the distance from the coronal hole boundary where the FIP bias changes and the gradient at this region. Based on that we study the diffusion of open field lines due to reconnection at the boundaries of coronal holes.

27 **Lee, Hyunkyu**
Postdoctoral Research Scientist, Biostatistics
"Liability Threshold Model-based Disease Risk Prediction Based on Electronic Health Record Phenotypes"

Electronic Health Records (EHR) have been increasingly adopted as useful resources for genomic research. However, case-control labeling of clinical data from EHR is challenging, and most studies utilize phenotype codes (PheCodes) to define case/control labels, resulting in suboptimal downstream analyses. Here we describe a new method, the Liability Threshold Phenotypic Integration (LTPI), to derive new phenotypes for a target disease by combining genetic relatedness information with phenotypic information,

spanning binary and continuous traits such as diagnosis codes, family disease history, laboratory measurements, and biomarkers. The model utilizes an automatic trait-selection algorithm that boosts computational efficiency, increases performance for disease risk prediction for the target disease, and provides insights into non-target traits associated with the target disease. In simulations and applications to the eMERGE network and the UK Biobank data, we found that LTPI consistently improves disease risk prediction accuracy and GWAS power across different scenarios relative to the conventional PheCode and models that solely incorporate family history.

28 **Li, Changan**
Postdoctoral Research Scientist, Chemical Engineering
"Light-Directed Spatial DNA Patterning for Selective Surface Material Loading"

Functional nanomaterials, including gold nanoparticles, quantum dots, and colloidal crystals, with their emergent properties at the nanoscale, hold significant potential in various fields, from optical sensing to drug delivery. However, developing a universal fabrication platform to harness these properties remains a challenge. Here, we demonstrated a fabrication method to enhance the scalability of material fabrication and establish a resilient foundation for the construction of complex multicomponent nano to macroscale architectures by integrating our DNA self-assembly platform with UV-directed DNA photolithography. Our approach involves chemically modifying the glass surface to create organic monolayers through advanced silane chemistry. The immobilization of DNA single strands will be achieved through a photochemical reaction. This involves generating patterns that integrate various pre-designed motifs and anchor sequences, thereby enabling a light-directed DNA self-assembly process on the surface with high spatial resolution. In contrast to conventional photo-crosslinking methods reliant on 'docking' strands that are pre-labelled to the target area functionalized with organic polymers through biotin and streptavidin binding, our approach simplifies the process and eliminates the need for chemical modification of both the 'docking' strand and its complementary DNA strand with photo-crosslinking organic moieties. DNA origami self-assembly platform utilizes frames that can be loaded with an arbitrary nanocargo, and through the programming of frame-frame and frame-surface interactions, we can direct the self-assembly and arrangement for nano-cargos of interest.

29 **Liang, Huiyi**
Postdoctoral Research Scientist, Department of Biomedical Engineering
"Tailored Yeast-derived Polyplexs for Oral CRISPR Cas9/dCas9 Delivery"

Effective delivery of CRISPR-Cas9/dCas9 elements is crucial to maximize therapeutic potential. Despite extensive efforts globally to improve delivery of gene editing elements for somatic genome editing, achieving gene editing via oral delivery has remained an elusive challenge. In this study, we present a novel orally-administered, nonviral gene editing system that offers exciting prospects for addressing the requirements of both local gene editing in the GI tract and systemic gene editing in a patient-friendly, non-invasive, and repeatable manner. By incorporating a yeast cell fragment into the polyplex, our oral nanoparticle platform for gene editing plasmids can efficiently traverse tightly packed

mucosal epithelium via intestinal microfold cells. Its subsequent endocytosis occurs in local and Peyer's patch macrophages, leading to a further accumulation in mesenteric lymph nodes (MLN). This strategy not only prolongs gene editing within the local GI tract and gut-associated lymphoid tissues but also facilitates transport through the gut-associated lymphoid pathway to the systemic circulation, ultimately modulating the genome of distal organs such as the liver. This culminates in the manifestation of titin gene activation in the small intestine and liver through oral administration with YF-CSNP. Our engineered delivery platform holds promise as a strategy for oral gene editing and activation, representing a significant advancement in the field with potential therapeutic applications.

30 **Lloyd, Caitlin**

Postdoctoral Research Fellow, Psychiatry

"Brain Volume within Frontostriatal Circuits Among Individuals with Anorexia Nervosa: A Longitudinal Investigation"

Background: Functional neuroimaging studies have identified abnormalities within frontostriatal circuits amongst individuals with anorexia nervosa (AN), both prior to and following weight restoration. Whether these functional differences are reflected in brain structure is unknown. This study characterized brain structure in specific frontostriatal regions of interest (ROIs; medial and lateral prefrontal cortex, rostral medial prefrontal cortex, striatum) at acute stages of AN (Time 1) and following weight restoration (Time 2).

Methods: Structural T1-weighted scans were combined across five studies. Participants were female patients with AN (Time 1: n=136, Time 2: n=58) and female healthy control peers (HC; n=113), aged between 12 and 40 years. Brain images were segmented into cortical and subcortical regions using the Freesurfer Desikan-Killany atlas; data were harmonized to remove scanner/site-related variance. Group differences in cortical thickness and volume within a-priori specified ROIs were examined using linear regression models adjusted for total gray matter volume, age, and study. Mass univariate testing (multiple comparison-corrected) was undertaken to examine group differences across all brain regions. Patients were compared to HC at Time 1 and Time 2.

Results: At Time 1, patients had reduced cortical thickness within all frontal cortical ROIs, and increased volume of the left caudate, relative to HC (p < 0.05). Mass univariate tests identified widespread reductions in cortical thickness among individuals with AN relative to HC at Time 1 (p < 0.05). No group differences were observed at Time 2.

Conclusions: Results of this study support structural alterations within frontostriatal circuits, as well as widespread reductions in brain volume, among individuals with AN at acute stages of illness. While the brain changes appear to resolve with weight restoration, multivariate analyses more sensitive to divergence from population norms are required to determine whether individuals with AN attain brain volumes within the range expected for developmental stage following renourishment.

31 **Mahato, Jaladhar**
Postdoctoral Research Scientist, Chemistry
"Machine Learning Unveils Complete Dipolar Orientations in AxiTIRF Defocused Imaging"

The orientation of molecules profoundly impacts the functional aspects of numerous advanced materials and biological processes. In most environments, the molecular organization is inhomogeneous and dynamic, posing challenges for traditional ensemble measurements. Single-molecule (SM) fluorescence microscopy is a promising approach to studying individual probe behaviors, circumventing issues related to ensemble averaging. Unfortunately, experimental extraction of 3D orientational information of molecular dipoles remains challenging.

While multichannel emission polarization detection strategies enable 3D orientation extraction, dipoles oriented largely out-of-plane remain inaccessible in traditional high-throughput widefield microscopy. SM-defocused imaging is an alternate approach that leverages slight movement of the microscope objective away from the focus to reveal characteristic spatial emission patterns that depend on molecular orientation. This approach, however, has two remaining problems. First, traditional illumination schemes either fail to excite out-of-plane dipoles or lack uniform excitation of in-plane dipoles. Moreover, in all implementations of SM-defocused microscopy, image analysis is computationally expensive, restricting its widespread adoption.

To address these limitations, two axicon-based total internal reflection (TIR) excitation schemes are adopted, capable of exciting dipoles in all orientations and generating characteristic image patterns. Additionally, a deep neural network is utilized to compare experimental axicon-based TIR fluorescence (AxiTIRF) patterns with theoretical images, facilitating the most accurate estimation of 3D orientation. We have applied this strategy to investigate the orientation of probe in polystyrene thin films near the glass transition temperature (T_g). The extracted angular information is utilized to evaluate the rotational dynamics of individual probes which report the local dynamics of the host typically obscured in the ensemble measurements. Furthermore, temperature-dependent experiments are conducted to characterize the dynamic heterogeneity at different temperatures. We anticipate that the precise quantification of angular displacement, as facilitated by our approach will provide insights into polymer dynamics and holds promise for shedding light on the unusual properties observed near T_g.

32 **Marshe, Victoria**
Postdoctoral Research Scientist, Neurology
"A Human Microglial Atlas of Expression Programs in Neurodegenerative Disease and Their Transcriptional Regulators"

Microglia show remarkable heterogeneity and complexity of transcriptional states in humans, which ultimately poses challenges to defining discrete molecular subtypes. In a large sample of live human microglia, our objective was to define a robust model of

transcriptional signatures, explore their associations with neuropathological outcomes in neurodegenerative disease, and identify a set of transcriptional regulators, with the goal of laying down the groundwork for a common nomenclature in microglia.

We performed single-cell RNA sequencing on tissue from 161 donors diagnosed with various neurological diseases (60% Alzheimer's disease), resulting in a dataset of 441,088 live microglial transcriptomes. Using scHPF, a Bayesian factorization method, we derived a model of continuous expression programs in microglia which were subsequently annotated to understand their biological and disease-associated relevance. Using ARACNe, we reconstructed a putative regulatory network comprising of 676 transcription regulators, four of which were prioritized as key regulators of the disease-associated microglia (DAM) signature and were selected for validation using a spatially-resolved (MERFISH) transcriptomic dataset of the dorsolateral prefrontal cortex.

We derived a 23-factor model which captures biologically relevant gene expression signatures, including the DAM2-like factor 26. To demonstrate the broad utility of the model, we projected external datasets onto our model, including human single-nucleus data, as well as in vitro and in vivo model systems, with and without biological, chemical, and genetic perturbations; however, none of the model systems fully captured the spectrum of observable human microglial signatures in our discovery dataset. Based on our putative regulatory network, we identified transcriptional regulators of the DAM2-like (26) program, particularly ARID5B and CEBPA which may be important regulators of the program.

Overall, our model shows biological relevance and points toward potential molecular mechanism associated with neuropathology. Ultimately, the model is broadly applicable and has the potential to provide a reference nomenclature for microglia.

33 **Martino, Jeremiah**

Associate Research Scientist, Medicine (Nephrology)

"Deletion of Crkl Splice Isoforms in the Mouse Kidney Disrupts Intercompartmental Signaling Required for Progenitor Renewal and Branched Morphogenesis"

We previously showed that haploinsufficiency and point mutations in CRKL drive kidney and urinary tract malformations in the DiGeorge, or 22q11.2, syndrome (DGS) and in sporadic CAKUT, respectively. Here, we examined the developmental requirement of the two Crkl splice variants (T1 & T2) when conditionally and differentially deleted in the metanephric mesenchyme (MM).

We characterized phenotypic abnormalities in developing kidneys from mice with conditional deletion of both T1 and T2 ("No Crkl"), or only the T1 isoform ("T2 only"), specifically within the MM. Bulk and scRNAseq data were acquired and analyzed from embryonic kidneys isolated from 13.5 and 15.5dpc wild-type and mutant mice. IHC and ISH analyses were used to validate and identify key signaling pathways.

At P0, both “No Crkl,” and “T2 only” kidney phenotypes were characterized by severe hypoplasia and near-absence of nephrogenic progenitors (NP). Morphometric analysis of the renal collecting system at 13.5 and 15.5dpc shows a hyperbranched phenotype in “No Crkl” mutants, while expression of only T2 led to a hypobranched phenotype. Using our single-cell data to “deconvolve” bulk RNAseq data, we found an overrepresentation of early proximal tubule (ePT) markers in “No Crkl” mice, and an underrepresentation in “T2-only” mice, suggesting a cell type-based contribution to the divergent branching phenotypes. Both groups of mutants also showed an underrepresentation of NP markers, where scRNAseq and ISH analyses confirmed decreased expression of Fgf8 and Fgf9 in NPs and renal vesicle. Lastly, in-depth time-based analyses of bulk RNAseq datasets revealed 3 differentially regulated gene sets that may explain the divergent branching phenotype between the two mutants.

Genetic manipulation of Crkl confirms a crucial role in kidney development, where disrupted Fgf8 expression suggests a cellular mechanism underlying renal hypodysplasia. Furthermore, disruption of splice isoform balance reveals a dichotomous pattern in early branching, suggesting a differential role for each isoform in regulating STOP and GO signaling associated with growth and branching morphogenesis.

34 **Mitra, Arijeet**
Postdoctoral Research Scientist, Environmental Health Sciences
“Groundwater Uranium Isoscapes to Trace Uranium Sources and Mobility in the Northern Plains”

Native American communities in the Northern Plains often rely on groundwater for drinking water, primarily sourced from private wells. Unfortunately, too many of these wells have more uranium than the safe drinking water limit set by the EPA. We are currently working with Missouri Breaks Industrial Research Inc (MBIRI), a tribally owned research organization, who partners with these communities to map the spatial patterns of uranium hotspots around the private wells in three reservations (Cheyenne River Sioux, Spirit Lake, and Oglala Sioux Tribes) in North and South Dakota. The release and removal of uranium in ground water typically depends on how oxidized the groundwater is. Natural uranium is composed of atoms that do not weigh the same. Some atoms are heavier than others, and the atoms with different weights are known as isotopes. The proportion of heavy isotopes relative to light ones is generally fixed. This proportion changes when uranium is released into water or removed from water. Additionally, the change in proportion of heavier isotopes to lighter ones also can inform the tribes about how far uranium has travelled from its source. We aim to study the proportion of heavier to lighter isotopes of uranium in water from private wells to understand whether uranium is actively added to or removed, and if it is from a local source or far away source. From this information, the goal is to create detailed maps of the hotspots of uranium release and removal. The preliminary results show that the amount of uranium in the groundwater varies widely with the highest concentration reaching about three times the EPA safe drinking water limit. Furthermore, data analyzed to date suggest distal sources of uranium relative to the private wells. These results will

ultimately help ensure the safe zones for drinking water for these Native American communities.

35 **Miura, Akihiro**
Postdoctoral Research Fellow, Medicine
"Lin28-Let7 Axis in Endothelial Cells Regulates the Heterochronicity in Interspecies Lung Generation via Conditional Blastocyst Complementation"

Millions of individuals worldwide are afflicted by incurable lung diseases, rendering lung transplantation a critical option for those in the end stages. However, the severe shortage of donor organs limits this option. One potential solution is the generation of human lungs in large animals through blastocyst complementation, a process currently impeded by interspecies barriers in host and donor cell development. In our previous work, we successfully generated complete lungs using conditional blastocyst complementation with mouse pluripotent stem cells (PSCs), rescuing the lethal phenotype of lung agenesis and enabling survival into adulthood. Building on this, we attempted to generate interspecies lungs by injecting rat PSCs into the mouse model. Although the lung agenesis phenotype was rescued by rat PSCs, the resulting chimeric lungs exhibited developmental delays, particularly around the canalicular stage, which were influenced by the regional rat chimerism in the lung mesenchyme but not in the lung epithelium.
We explored the role of the heterochronic gene Lin28, known to regulate developmental timing in C. elegans and mice, in interspecies chimeric lung generation. In regions with high rat chimerism, we observed an upregulation of Let7 and a significant decrease in Lin28 expression in the Tie2+ capillary plexus. Moreover, overexpression of Let7 in rat capillary endothelial cells led to decreased Tie2 expression and reduced cellular migration. Co-culture experiments with rat capillary endothelial and mouse epithelial cells showed that high Let7 expression hindered lung epithelial organoid formation by affecting the survival of lung epithelial cells. Our findings suggest that the heterochronicity in lung development between epithelial and mesenchymal compartments is regulated by lung endothelial cells through the Lin28-Let7-Tie2 axis. These insights pave the way for future therapies involving the generation of human lungs in large animals.

36 **Moeller, Cathrine**
Postdoctoral Research Fellow, Medicine (Cardiology)
"Enhancing the understanding of Elevated Donor-Derived Cell-Free DNA in Heart Transplant Recipients in a Biopsy-Negative cohort"

Introduction: This study investigates the clinical implications of a positive Donor-derived Cell-Free DNA (dd-cfDNA) findings in heart transplant (HT) recipients who exhibit negative biopsy findings, aiming to clarify the role of dd-cfDNA as a predictive marker for post-transplant outcomes.

Methods: We retrospective analyzed dd-cfDNA samples from all consecutive HT recipients between 2019 to 2023, excluding those with multiorgan transplants. Each sample were correlated with a recent endomyocardial biopsy (EMBx), performed within

1 month. A positive biopsy was defined based on International Society for Heart and Lung Transplantation (ISHLT) criteria of ³1R/1B or pAMR>0. Dd-cfDNA result of ≥ 0.12% were considered positive, with graft dysfunction defined by an ejection fraction <50%. We excluded dd-cfDNA samples with concurrent histologically positive biopsy results, focusing our analysis on the discordant group with positive dd-cfDNA and negative biopsy findings.

Results: Out of 643 dd-cfDNA samples from 227 patients, 238 samples (37%) from 110 patients showed positive dd-cfDNA results. The median age was 56 years, with 27% females and 53% white individuals. The median time from transplant to sample collection was 5 months IQR [3,12] months, and the median dd-cfDNA level in the positive samples was 0.24% IQR [0.16%, 0.53%]. Notably, 63% of the positive samples exceeded 0.20% dd-cfDNA. A higher prevalence of prior treated AMR was observed in the dd-cfDNA positive group (15% vs 5%; p<0.001). A significantly worse survival was found at 2-years in the positive group compared to the negative (91% vs. 97%; log-rank; p=0.013). Cox-regression analysis demonstrated that patients with a positive dd-cfDNA results was associated with a doubled risk of mortality (HR 2.3; 95% CI (1.2 - 4.4); p=0.016) and a nearly quadrupled risk of graft dysfunction (log rank test, p<0.001; HR 3.8; 95% CI (1.7-8.5); p=0.001) compared to negative counterparts.

Conclusion: Positive dd-cfDNA levels in HT recipients, despite negative biopsy results, significantly predict a heightened risk of graft dysfunction (almost 4-fold) and increased mortality (2-fold).

37 **Muniz de Queiroz, Rafaela**
Associate Research Scientist, Biological Sciences
“MDM2 Regulates Metastasis by Modulation of Sprouty4 Independent of p53”

Mdm2 and its homologue MdmX form an E3-ligase complex that is best understood as the major regulator of p53. Yet Mdm2 and MdmX have functions in cells that are independent of their ability to degrade p53. Amongst the functions regulated by Mdm2 is cell migration, although the molecular mechanism(s) involved have not been well characterized. We show here that either siRNA knockdown of Mdm2 or MdmX as well as pharmacological inhibition of the Mdm2/X complex E3-ligase activity in cells that lack expression of p53, can reduce migration of cells grown as monolayer or invasion of cells from pre-formed spheroids into a hydrogel matrix. Accordingly, silencing of Mdm2 also decreases metastatic capability of cancer cells in vivo. We observed that Mdm2 ablation or inhibition leads to decreased cell spreading and attachment of cells to the extracellular matrix. In line with these findings, we also found that modulation of Mdm2, MdmX or the Mdm2/X complex impacts focal adhesion (FA) formation, a main step in cell attachment, spreading and migration. Mechanistically, we have discovered that Mdm2 modulates the expression of Sprouty4 and that Sprouty4 is needed for the effects of Mdm2 knockdown on cell migration, FA formation and metastasis. Taken together, we have discovered a pathway by which Mdm2, through the activity of the Mdm2/X complex, mitigates FA formation, cell invasion and metastatic disease by regulation of Sprouty4 independently of p53. Our findings suggest that blocking Mdm2 or the

Mdm2/X heterocomplex is a potential strategy for the treatment of tumors in late stages of the disease (metastatic disease) even in patients that had lost wild type p53.

38 **Nadezhdin, Kirill**
Postdoctoral Research Scientist, Biochemistry and Molecular Biophysics
"Unlocking TRPV3: How Small Molecules Activate the Molecular Temperature Sensor"

TRPV3 represents both temperature- and ligand-activated transient receptor potential (TRP) channel. Physiologically relevant opening of TRPV3 channels by heat has been captured structurally, while opening by agonists has only been observed in structures of mutant channels. We present cryo-EM structures that illuminate opening and inactivation of wild-type human TRPV3 in response to binding of two types of agonists: either the natural cannabinoid tetrahydrocannabivarin (THCV) or synthetic agonist 2-aminoethoxydiphenylborane (2-APB). THCV binds to the vanilloid site, while 2-APB binds to the S1-S4 base and ARD-TMD linker sites. Despite binding to distally located sites, both agonists induce similar pore opening and cause dissociation of a lipid that occupies the vanilloid site in their absence. Our results uncover different but converging allosteric pathways through which small-molecule agonists activate TRPV3 and provide a framework for drug design and understanding the role of lipids in ion channel function.

39 **Ogidigo, Joyce**
Postdoctoral Research Scientist, Medicine (Preventive Medicine)
"Understanding the Role of Overnutrition and Glycation in Lung Cancer"

Background: Lung cancer presents a significant health burden, contributing substantially to cancer-related mortality due to its poor survival rates. The Western diet, characterized by high fat and sugar content, is implicated as a primary driver of cancer progression and treatment inefficacy. Despite numerous studies highlighting the detrimental effects of these dietary components on disease advancement, the precise molecular mechanisms linking excessive nutrient intake to lung cancer progression remain elusive.

Hypothesis: Therefore, we hypothesized that a hypercaloric diet could exacerbate KrasG12D/+-dependent non-small cell lung cancer (NSCLC) progression in vivo. To test our hypothesis, we utilized a trackable genetic mouse model (GEMM) of lung cancer to examine the role of overnutrition-dependent remodeling of lung tumors across various stages of LUAD. Tumor-bearing mice were subjected to different diet regimes, including standard diet (SD) and Western diet (WD), comprising a high-fat diet (HFD) and high-sugar water. We monitored tumor development via PET/CT imaging and conducted molecular analyses at distinct stages and histological examinations.

Results: Our findings reveal that tumor-bearing mice on the Western diet exhibited decreased overall survival, accelerated tumor growth, and increased lung tumor metabolism and progression in the KrasG12D/+/p53fl/fl LUAD mouse model, as evidenced by heightened fluorine-18-fluorodeoxyglucose (FDG) uptake. Furthermore, we identified a Western diet-induced transcriptional signature that independently predicts lung cancer progression and mortality.

Conclusion: Taken together, our data demonstrate that the Western diet promotes lung cancer progression through modulation of key molecular pathways and metabolic alterations in KRAS-dependent NSCLC. Given the prevalence of this malignancy and the challenges associated with therapeutically targeting KRAS signaling, our findings may hold significant translational implications for lung cancer treatment.

40 **Pérez Ortega, Jesús**
Postdoctoral Research Scientist, Biological Sciences
"Inhibition Enhances Encoding Precision of Neuronal Ensembles in Mouse Visual Cortex"

Neuronal ensembles are groups of neurons with correlated activity associated with sensory, motor, and behavioral functions. To explore how ensembles encode information, we investigated responses of visual cortical neurons in awake mice using volumetric two-photon calcium imaging during visual stimulation. We identified neuronal ensembles employing an unsupervised model-free algorithm and, besides neurons activated by the visual stimulus (termed "onsemble"), we also find neurons that are specifically inactivated (termed "offsemble"). Offsemble neurons showed faster calcium decay during stimuli, suggesting selective inhibition. In response to visual stimuli, each ensemble (onsemble+offsemble) exhibited small trial-to-trial variability, high orientation selectivity, and superior predictive accuracy for visual stimulus orientation, surpassing the sum of individual neuron activity. Thus, the combined selective activation and inactivation of cortical neurons enhance visual encoding as an emergent and distributed neural code.

41 **Pulupa, Joan**
Postdoctoral Research Scientist, Zuckerman Institute
"Live-cell Microscopy Enables a Mechanistic Interrogation of Olfactory Receptor Gene Regulation in Olfactory Neurons"

Detection and identification of volatile chemicals in the mammalian olfactory system is built upon the "one receptor per neuron" rule, whereby each mature olfactory sensory neuron expresses a single olfactory receptor (OR) gene from over 2,000 possible alleles. Singular expression is critical for olfactory perception, defining both the receptive field of the OSN and the circuitry of its axon. This singular expression is contingent on orchestrated changes in nuclear architecture.

OR gene activation is accomplished by the formation of a hub that brings together loci from various chromosomes and associates with and activates a single OR gene. This hub forms under the control of the transcription factors, Lhx2 and Ebf, and the adaptor protein Ldb1. I have fluorescently labeled the genomic loci of the expressed OR and these regulatory proteins, allowing me to monitor their dynamics in living primary mouse neurons.

The formation of this hub allows the chosen OR to overcome repression, and this hub represents a greater enrichment of transcription factors than can be explained simply by the stoichiometry of enhancer binding sites within the hub. With single-particle tracking and super-resolution imaging, I have characterized the biomolecular interactions that allow the hub to recruit and concentrate Lhx2/Ebf/Ldb1 specifically at the genomic loci of the expressed OR. In extending my research towards a complete characterization of the nucleoprotein dynamics regulating OR gene expression, I have begun to characterize the interactions of OR enhancers and OR mRNA with Lhx2/Ebf/Ldb1 using super-resolution imaging.

42 **Qi, Ning**
Postdoctoral Research Scientist, Earth & Environmental Engineering
"Chance-Constrained Generic Energy Storage Operations under Decision-Dependent Uncertainty"

Compared with large-scale physical batteries, aggregated and coordinated generalized energy storage (GES) resources provide low-cost, but uncertain, flexibility for power grid operations. While GES can be characterized by different types of uncertainty, the literature mostly focuses on decision-independent uncertainties (DIUs), such as exogenous stochastic disturbances caused by weather conditions. Instead, this manuscript focuses on newly-introduced decision-dependent uncertainties (DDUs) and considers an optimal GES dispatch that accounts for uncertain available state-of-charge (SoC) bounds that are affected by incentive signals and discomfort levels. To incorporate DDUs, we present a novel chance-constrained optimization (CCO) approach for the day-ahead economic dispatch of GES units. Two tractable methods are presented to solve the proposed CCO problem with DDUs: (i) a robust reformulation for general but incomplete distributions of DDUs, and (ii) an iterative algorithm for specific and known distributions of DDUs. Furthermore, reliability indices, i.e., loss-of-response probability and expected response energy not served, are introduced to verify the applicability of the proposed approach with respect to the reliability of the response of GES units. Simulation-based analysis shows that the proposed methods yield conservative, but credible, GES dispatch strategies and reduced penalty cost by incorporating DDUs in the constraints and leveraging data-driven parameter identification. This results in improved availability and performance of coordinated GES units.

43 **Rahman, Salwa**
Postdoctoral Research Fellow, Medicine (Cardiology)
"Sublingual Microcirculation in acute Mechanical Circulatory Support in Cardiogenic Shock"

Introduction: Acute mechanical circulatory support (AMCS) is increasingly used in the management of cardiogenic shock to restore end organ perfusion. Little is known about the impact of AMCS on the microcirculation. The objective of our study was to characterize the impact of different AMCS devices on the microcirculation.

Method: We included patients who were admitted with CS and supported with AMCS with or without vasoactive medications from May to September, 2023. Microcirculation parameters were measured sublingually utilizing the novel GlycoCheck™ microvascular imaging system and analysis software. Severity of CS was defined by Cardiogenic shock working group-SCAI stage. Microcirculation parameters were compared across AMCS devices using Mann-Whitney U test.

Result: A total of 37 CS patients supported with AMCS were included in the analysis. Mean age was 66 (SD +/-12) years and 58% were male. The most common causes of CS were acute decompensated heart failure (67%) and acute MI (20%). At the time of imaging, 33% patients were SCAI C, 52% SCAI D, and 15% SCAI E CS; 11 patients were supported with VA-ECMO with or without another AMCS, 10 with Impella 5.5 and 16 with IABP. Patients with V-A ECMO demonstrated significantly lower total density of 4-25µm functional vessels (p=<0.001), total number of 4-6 µm capillaries(D4-6) (p=<0.001), dynamic capillary blood volume (CBVD, p=0.01), blood flow (p=<0.001) and microvascular health score (MVHS, p=0.001) compared to patients on Impella 5.5 or IABP.

Conclusion: In our series of CS patients on AMCS, patients on V-A ECMO had increased impairment of microcirculation when compared to patients on Impella 5.5 or IABP. Additional studies are warranted to better characterize the impact of AMCS on microcirculation.

44 **Rocha Monteiro de Barros, Maithe**
Postdoctoral Research Scientist, Irving Institute for Cancer Dynamics
"Simultaneous Profiling of Gene Expression and Chromatin Accessibility in the Study of Gastric Cancer Development"

Gastric cancer (GC) is the fifth leading cause of cancer death worldwide. Gastric adenocarcinomas (GACs) are classified into diffuse and intestinal GC. Their initiation is often associated with inactivation of CDH1 and TP53 genes, respectively. Furthermore, environmental factors such as dietary nitrate intake and Heliobacter pylori infection contribute to the development of GACs. Nonetheless, the cells of origin and mediators of progression in GACs are not well understood. Studies of GACs initiation are hampered by the limited availability of and detailed characterization of GC mouse models. This study aims to generate and perform characterization of novel mouse models of GC, initially focusing on healthy gastric tissue.

Healthy gastric tissue samples from three female and three male mice were analyzed using single-cell multiome (scMultiome) assay that simultaneously profiles RNA expression and chromatin accessibility (ATAC-seq) at the single-cell level. Nuclear hashing was used to uniquely label cells originating from distinct biological samples. Data analysis was performed in R using the Seurat and Signac packages.

After data processing and quality control, 14790 cells were analyzed (average of 2465 per animal). Smart local moving clustering for combined RNA and ATAC-seq signals

identified all known gastric epithelial cell types. The incorporation of the ATAC-seq signal improved the resolution of cell type annotation and identified new cell subpopulations. Trajectory analysis supports Isthmus/Neck cells are most likely stem-like cell population of gastric epithelium. We further identified novel fibroblast populations that can potentially support gastric stem cell niche.

Our findings highlight the value of scMultiome in capturing comprehensive gene expression and epigenetic information, revealing gene regulatory interactions and a better interpretation of epigenetic profiles. Future combined trajectory analysis using RNA and ATAC-seq data will shed further light on the differentiation processes shaping gastric epithelium. Subsequent expansion of analysis to include genetic mouse models will inform the identity of GC cell-of-origin.

45 **Roy, Tuhin**
Postdoctoral Research Scientist, Biomedical Engineering
"Viscoelasticity Estimation Using Physics-Informed Neural Network for Breast Shear Wave Elastography"

Background:
Breast Shear Wave Elastography (SWE) is a non-invasive technique using acoustic radiation force to characterize tissue stiffness for breast cancer detection and thermal ablation monitoring. While conventional SWE faces challenges in heterogeneous soft materials due to wave diffraction, this study introduces a Physics-Informed Neural Network (PINN) based Inverse model[1]. Unlike computationally expensive Finite Element (FE) models, PINN solves the governing partial differential equation (PDE) without discretization, offering a promising alternative for estimating viscoelastic shear moduli.

Method:
The proposed model's PDE incorporates spatial variation of elastic modulus, encoded in the PINN structure as a loss function. Since the soft tissues are nearly incompressible, we consider only the shear wave term in the Helmholtz PDE as the deformation due to the pressure wave is close to constant[2]. The Kelvin-Voigt model is employed to simulate viscoelasticity. Data loss term focuses on the misfit of particle velocity in axial (Z) direction, aligning with conventional SWE experiments.

Utilizing wave motions, a PINN model infers viscoelastic moduli in a shear wave-illuminated region. The model comprises two deep neural networks (NN1 and NN2) with three hyper-parameters: $\lambda 1$, $\lambda 2$ (weight parameters), and η (viscosity in Pa.s). NN1 predicts particle displacement in the Z direction based on spatial coordinates (X, Z) and time (T). NN2 predicts shear modulus (unit kPa) at each spatial coordinate (X, Z). NN1 has 6 hidden layers with 30 neurons each, while NN2 has 2 hidden layers with 15 neurons each, both using tanh as the activation function.

The PINN-based model has an advantage over conventional SWE methods in that it can seamlessly integrate multi-source data into the inverse model. Therefore, we analyze data

from Pulse-SWE and Harmonic-SWE[3] experiments and combine tissue deformations from excitations at different points. For validation, we perform FE simulations, tissue-mimicking phantom and ex vivo experiments.

Results:
In a homogenous medium, the proposed framework achieves a shear modulus of 13.16 kPa and viscosity of 0.20 Pa.s, closely matching FE simulation inputs of 14.3 kPa and 0.23 Pa.s. In a heterogeneous scenario, the shear modulus converges to 108.02 kPa at the stiffer inclusion, 12.88 kPa at the background, and shear viscosity converges to 0.25 Pa.s for both inclusion and background. The corresponding FE simulation inputs are 118.8 kPa for inclusion, 14.3 kPa for the background, and 0.23 Pa.s for both inclusion and background. In terms of efficiency, the PINN analysis completes in approximately 12 minutes for 3000 epochs.

46 **Sepulveda Delgado, Pradyumna**
Postdoctoral Research Scientist, Psychiatry
"Reward Anticipation and Information Seeking as a Transdiagnostic Target in Psychopathology"

An influential idea in behavioral economics is that people derive pleasure from the moments leading up to a reward in addition to the reward itself (anticipatory utility, Loewenstein, 1987). Recent studies integrating a computational model of reward anticipation with an established information-seeking paradigm (Bromberg-Martin and Hikosaka, 2009) have suggested that humans prefer to obtain advanced information about future outcomes to enhance their experience of anticipation (Iigaya et al., 2016; 2020). However, to our knowledge, this anticipatory utility framework has not been applied to understand psychiatric conditions. In this work, using a transdiagnostic approach, we validate the suitability of the information and reward anticipation task across self-reported psychopathology in a sample of online participants. In a web-based version of the task we developed, participants were first informed in each trial about the time delay prior to the delivery (or lack thereof) of a video reward. Participants could then choose to either receive immediate information or opt to remain uninformed about the upcoming result. Visual cues reflecting that choice, by either communicating or withholding the future outcome, would then remain onscreen for the duration of the delay; participants experienced the delay irrespective of the choice they made. In our setup, rewards were compelling videos in participants' preferred category (e.g., cute puppies), allowing for immediate consumption upon delivery. Participants displayed a wide range of information-seeking patterns. We found that participants who preferred to obtain advanced information about the outcome self-reported higher levels of anticipatory pleasure in established questionnaires. In a factor analysis that separated relevant psychopathology dimensions across multiple questionnaires, we found that higher expression of an Apathy-Anhedonia dimension was present in participants with lower information-seeking preference in the anticipation task. Our findings suggest that this new approach can offer quantitative behavioral measures for reward anticipation (RDoC construct) deficits, commonly expressed across clinical populations.

47 **Shah, Vikash Kumar**

Postdoctoral Research Scientist, Medicine (Pulmonary Medicine)

"Reduced Endothelial Protection Against Complement in Obstructive Sleep Apnea: A Protective Function of Derlin-1"

RATIONALE:

Obstructive sleep apnea (OSA) triples cardiovascular risk. OSA-related intermittent hypoxia (IH) triggers endothelial cell (EC) inflammation by increasing internalization of complement inhibitor CD59, a cholesterol-dependent process that reduces protection against complement. IH-induces ER stress, which impairs cholesterol trafficking in ECs. We have identified Derlin-1 as an ER-bound ligand for VAMP-associated protein-B (VAPB) that displaces oxysterol binding protein-related protein-1L (ORP1L) in IH, which impairs cholesterol trafficking in ECs in IH and OSA. Whether Derlin-1-VAPB interaction mediates protection against complement in ECs during IH is unknown. We hypothesized that altered Derlin-1-VAPB interaction impairs cholesterol trafficking in ECs during IH, which reduces endothelial protection against complement thereby increasing cardiovascular risk in OSA.

METHODS:

Derlin-1 was silenced using siRNA in human umbilical vein endothelial cells (HUVECs) exposed to IH (alternating 30 min 21% O2 /30 min 2% O2 for 8h). Intracellular free cholesterol, lipid droplets, internalization of complement inhibitor CD59, membrane attack complex (MAC) deposition, and nuclear fluorescence of nuclear factor κB (NFκB) were quantified by immunofluorescence and confocal microscopy.

RESULTS:

In IH, silencing Derlin-1 reduced intracellular free cholesterol (n=5; mean±SEM fluorescence intensity [arbitrary units; au] 1063±72.4 vs. 1380.2±58.6, p=0.007) and increased lipid droplets (n=6; mean±SEM; fluorescence area/cell [μm2], 0.37±0.02 vs. 0.17±0.01, p=0.0001) compared to control siRNA. Derlin-1 silencing reduced endothelial CD59 internalization (n=4; mean±SEM; colocalized area of endocytosed CD59 with flotillin-1 area/cell [μm2], 0.3±0.009 vs. 0.63±0.06, p=0.001), MAC deposition (n=6; mean±SEM; fluorescence area/cell [μm2], 0.5±0.05 vs. 0.72±0.06, p=0.008) and NFκB nuclear fluorescence (n=4; mean±SEM fluorescence intensity [arbitrary units; au] 1781.02±211 vs. 3026.24±173.6, p=0.002) compared to control siRNA in IH.

CONCLUSIONS:

Silencing Derlin-1, an ER-bound VAPB ligand that impairs EC cholesterol trafficking in IH and OSA, restores endothelial protection against complement and reduces inflammation in IH.

48 **Shin, Alice**

Postdoctoral Research Scientist, Herbert Irving Comprehensive Cancer Center

"Exploring the Efficacy of Alpelisib and Combined PI3Kα-S6K Inhibition in Metastatic Colorectal Cancer"

Colorectal cancer (CRC) is the third most diagnosed cancer globally. Our lab has identified LIN28B, an RNA-binding protein, as a promoter of CRC metastasis. However, the mechanisms through which LIN28B promotes CRC metastasis remain unclear. The phosphatidylinositol 3-kinase (PI3K)/AKT pathway, primarily activated by the downstream effector ribosomal protein S6 kinase (S6K), is crucial for cell growth and protein synthesis. PIK3CA mutations, seen in 20-30% of CRC cases, lead to the activation of the PI3Kα enzyme, correlating with poor CRC prognosis. Despite the prevalence of PIK3CA mutations, targeted therapies for PIK3CA-mutant CRC are lacking. Alpelisib, a PI3Kα inhibitor FDA-approved for a subset of PIK3CA-mutant breast cancers, remains largely unassessed in CRC.

Our data indicate that LIN28B expression in CRC cells promotes liver metastasis in mouse models of metastatic CRC (mCRC) and activates the PI3K/AKT pathway, as evidenced by an AKT phosphorylation array. Treatment with SC79, a pan-AKT activator, enhances cell migration and invasiveness. This activation pattern is mirrored in VillinCreERT;R26Pik3ca mice, expressing a constitutively active form of PI3Kα in the intestinal epithelium, resulting in crypt hyperplasia, enhanced tumorigenesis, and liver metastasis. Notably, Alpelisib effectively hinders LIN28B-driven CRC progression in cell lines, transgenic mice-derived organoids, mCRC mouse models, and CRC patient-derived organoids (PDOs). The effects observed with Alpelisib treatment are replicated upon inhibiting S6K with LY25284702. Furthermore, combining low-dose Alpelisib with LY25284702 synergistically restricts the growth of CRC PDOs. Reinforcing these findings, an analysis of a tissue microarray from 60 patients showed elevated PI3K/AKT/S6K signaling in liver metastases compared to primary tumors or normal colonic tissues.

These findings underscore the role of the PI3K/AKT pathway in LIN28B-mediated CRC metastasis and suggest Alpelisib as a potential targeted therapy for PIK3CA-mutant CRC. Our study also highlights the efficacy of combining targeted inhibitors to improve anti-metastatic outcomes.

49 **Shin, Heegwon**
Associate Research Scientist, Microbiology and Immunology
"Long 3`UTR Establishes Neuronal-specific Anti-viral Status by Facilitating Immunostimulatory Double-stranded RNA Formation"

Exogeneous double-stranded RNAs (dsRNA) are well documented as innate immune response initiators when detected by host pattern recognition receptors (PRRs). dsRNA imbalance sensitively affects neurons, thereby contributing to neurodegenerative and neuroinflammatory diseases. Here, we found that neurons are a special cell type with exceptionally high levels of dsRNAs. We identified that neuro-specific 3`UTR lengthening by HuB, HuC, and HuD proteins contributes to dsRNA accumulation. Surprisingly, these high levels of dsRNA in neurons generate a tonic level of type I interferon through the dsRNA-PRR axis without any types of infections. Lastly, we confirmed that neurons build a unique anti-viral environment by these pre-existing type I

interferons. In summary, as a distinguished cell type, neurons maintain a high basal antiviral state through constant PRR activation via endogenous dsRNAs.

51 **Soni, Mithil**
Associate Research Scientist, Medicine (Hematology & Oncology)
"Multi-epitope Specific Cytotoxic CD4+ T Cells for Adoptive Immunotherapy of Myelodysplastic Syndrome"

Myelodysplastic Syndromes (MDS) are complex blood disorders characterized by ineffective blood cell production and a risk of progressing to acute myeloid leukemia (AML). Treatment options are limited, especially for older patients, with hematopoietic stem cell transplant being the only curative option, but often unsuitable due to age or relapse risks. Hypomethylating agents offer modest benefits to some patients. Novel therapies are urgently needed. Recent studies have shown promise in adoptive immunotherapy using T cells targeting specific antigens in AML. However, these studies primarily focused on CD8+ T cells, overlooking the potential of CD4+ T helper (Th) cells which play a crucial role in immune responses. Our animal model research indicated that antigen-specific CD4+ T cells could effectively eliminate tumors. In this study, we investigated the feasibility of generating autologous CD4+ T cells targeting multiple tumor-associated antigens (TAAs) for MDS and AML patients. We developed a novel ex vivo priming method using dendritic cells loaded with TAAs to activate CD4+ T cells. These cells were then expanded using pro-inflammatory cytokines. Results showed that CD4+ T cells cultured under pro-inflammatory conditions exhibited significantly increased reactivity against TAAs compared to conventional methods. These cells also showed enhanced expansion, polyfunctionality, and proliferative capacity upon repetitive stimulation. Importantly, they recognized naturally processed antigens, indicating their clinical relevance. Furthermore, we successfully generated multi-TAA-specific CD4+ T cells from MDS patients, demonstrating similar enhanced characteristics as seen in healthy individuals. In conclusion, our study demonstrates that ex vivo priming with TAAs in the presence of pro-inflammatory cytokines can reliably generate CD4+ T cells with enhanced specificity, functionality, and cytotoxic potential. These findings offer promising prospects for developing improved adoptive immunotherapies for myelodysplastic syndrome and related conditions.

52 **Srivastava, Prashast**
Postdoctoral Research Scientist, Computer Science
"FOX: Coverage-guided Fuzzing as Online Stochastic Control"

Fuzzing is an effective technique for discovering software vulnerabilities by generating random test inputs and executing them against the target program. However, fuzzing large and complex programs remains challenging due to difficulties in uncovering deeply hidden vulnerabilities. This paper addresses the limitations of existing coverage-guided fuzzers, focusing on the scheduler and mutator components. Existing schedulers suffer from information sparsity and the inability to handle fine-grained feedback metrics. The mutators are agnostic of target program branches, leading to wasted computation and slower coverage exploration.

To overcome these issues, we propose an end-to-end online stochastic control formulation for coverage-guided fuzzing. Our approach incorporates a novel scheduler and custom mutator that can adapt to branch logic, maximizing aggregate edge coverage achieved over multiple stages. The scheduler utilizes fine-grained branch distance measures to identify frontier branches, where new coverage is likely to be achieved. The mutator leverages branch distance information to perform efficient and targeted seed mutations, leading to robust progress with minimal overhead.

We present FOX, a proof-of-concept implementation of our control-theoretic approach, and compare it to industry-standard coverage-guided fuzzers. 5 CPU years of extensive evaluations on the FuzzBench dataset and complex real-world programs (a total of 33 test programs) demonstrate that FOX outperforms existing state-of-the-art fuzzers, achieving average coverage improvements up to 24.26% in real-world standalone programs and 10.97% in Fuzzbench programs over the state-of-the-art AFL++. In addition, it uncovers 20 unique bugs in popular real-world applications including eight that are previously unknown showcasing real-world security impact.

53 **Waller, Bernadine**

Postdoctoral Research Fellow, Psychiatry

"Engaging Community Stakeholders in Tailoring an Evidence-based Intervention for US Black Women Survivors with Depression Help-seeking in Faith-based Organizations"

Background: United States (US) Black women intimate partner violence (IPV) survivors with depression experience the poorest outcomes among all racial/ethnic women; yet few interventions address their nuanced needs. Depression is particularly pernicious for IPV survivors. And it is especially harmful among women with intersectional identities. Current interventions are largely failing. Black women reflect low uptake and high attrition. Centering their needs in intervention development may improve treatment adherence.

Methods: An interdisciplinary team of 16 stakeholders (e.g., diverse group of Black IPV survivors, including veterans, Afro Caribbean, and women with a physical disability; clergy; IPV advocates; and mental health clinicians), partnered with us. Workgroup participants were recruited from a larger formative study to understand how to implement an evidence-based intervention (EBI) for Black women survivors with depression help-seeking in faith-based organizations (FBOs). The PRISSMA framework was employed to 1) review existing EBIs; 2) ensure culturally responsiveness; and 3) provide recommendations for tailoring the EBI. Workgroup members consented to session recording prior to participating. Transcribed data was triangulated via demographic surveys and field notes.

Results: Findings underscore the urgent need to center Black survivors' needs. Findings suggest that they prefer a brief (<6 sessions) EBI for depression that can be delivered by providers with similar lived experiences in faith-based organizations. We further found that survivors prefer interventions that infuse their faith, account for social

determinants of health and allow for in-person and virtual options. Importantly, fundamental to delivering a successful IPV intervention for depression is including psychoeducation about IPV and depression to increase awareness and understanding.

Conclusion: This is the first to employ the PRISSMA framework for tailoring a culturally responsive EBI for Black women IPV survivors presenting with depression. Findings suggest that tailoring a brief intervention that is responsive to their nuanced needs will increase treatment adherence and improve uptake.

54 **Wu, Xun**
Postdoctoral Research Scientist, Medicine (Cardiology)
"Pushing the Limits of Macrophage Efferocytosis in Atherosclerosis"

Introduction: Enhancing macrophage efferocytosis represents a potential therapeutic strategy for residual risk reduction in atherosclerotic cardiovascular disease. Our genome-wide CRISPR screening discovered Pdcd6ip as a top-ranked negative regulator of efferocytosis. PDCD6IP, also known as ALIX, is an accessory protein of ESCRT machinery, regulating multivesicular body formation and cytokinesis. Yet, how PDCD6IP may act as a molecular break on macrophage efferocytosis has not been characterized.

Goals: Determine if knockout of Pdcd6ip enhances macrophage efferocytosis and protects against atherosclerosis pathogenesis.

Methods: In vitro efferocytosis assays were performed in bone marrow-derived macrophages (BMDMs) and human monocyte-derived macrophages (HMDM). In vivo studies involved Ldlr-/- recipient mice with bone marrow transplantation (BMT) of WT and Pdcd6ip-/- BMs.

Results: Pdcd6ip-/- induces cytokinesis arrest in proliferating BMDMs, resulting in an increased formation of binuclear polyploid BMDMs. Binuclear BMDMs have a remarkable capacity to engulf multiple apoptotic cells (ACs), termed continuing efferocytosis. While both mononuclear and binuclear Pdcd6ip-/- BMDMs demonstrate enhanced efferocytosis in primary efferocytosis, binuclear Pdcd6ip-/- BMDMs show enhanced continuing efferocytosis compared to binuclear WT BMDMs. Pdcd6ip-/- BMDMs have increased phagolysosomal acidification of the engulfed ACs, implicating proper degradation. Pdcd6ip-/- did not alter the engulfment of live cells, beads, or zymosan, supporting specific regulation of AC clearance. We hypothesize that Pdcd6ip-/- will be protective in atherosclerosis. Indeed, BMT of Pdcd6ip-/- BMs into Ldlr-/- mice led to increased atherosclerotic plaque stability after 22 weeks of Western diet feeding, characterized by decreased necrotic core area and increased fibrous cap thickness, without affecting the overall lesion area. Knockdown of PDCD6IP in HMDMs also led to an increased formation of binuclear HMDMs and enhanced continuing efferocytosis.

Conclusion: We discovered a new role of PDCD6IP as a molecular break of macrophage efferocytosis. Inhibiting macrophage PDCD6IP may represent a therapeutic opportunity in atherosclerosis.

55 **Yan, Na**
Postdoctoral Research Scientist, Biomedical Engineering
"Artificial Probiotic Biofilm for Periodontitis Treatment"

Periodontitis, a prevalent oral disease primarily attributed to microbial imbalances within the oral cavity, has a high global incidence. Conventional pharmacological treatments for periodontitis typically involve broad-spectrum sterilization with antibiotics, which present certain therapeutic limitations. In this study, we propose probiotic therapy as an alternative approach to treat periodontitis by rebalancing the oral microbiota through increased probiotic proportions. We focused on utilizing K12 probiotics, known for secreting bacteriostatic substances Salivaricin A and Salivaricin B, which can remove or reduce the proportion of harmful bacteria, such as Porphyromonas gingivalis, the primary pathogenic bacteria in periodontitis. To enhance probiotic colonization and bolster their protective effects, we developed an artificial probiotic biofilm dry powder spray. The probiotic bacteria (K12) surfaces were chemically modified with polymers to serve a triple function: firstly, facilitating probiotic colonization on various oral surfaces including gingival tissue, existing biofilm, and tooth surfaces; secondly, forming a hydrogel to shield the adhering probiotics; thirdly, incorporating a hydrophilic component into the polymer to create a hydrophilic layer on the outermost surface of the hydrogel, thereby preventing re-adhesion of other bacteria to the probiotic biofilm surface. Experimental studies conducted on mice and pigs demonstrated the efficacy of our probiotic biofilm in both preventing and treating periodontitis. These findings suggest the potential of our approach as a promising therapeutic strategy for periodontal disease management.

56 **Yi, Ming**
Postdoctoral Research Scientist, Data Science Institute
"Decision-Focused Prediction of Strategic Energy Storage Behaviors"

With the rapid increase in grid-scale energy storage deployment, it has become crucial for power system operators to accurately predict strategic energy storage behaviors in electricity markets, specifically the timings of charging and discharging. This prediction task is complex due to the intricate interplay of market fluctuations and decision-making processes, constrained by physical power and energy limits. We introduce a novel, decision-focused, end-to-end methodology that directly forecasts storage charge and discharge profiles at sub-hourly resolutions, leveraging past pricing data and storage activity. This approach does not rely on future price predictions or intermediary price forecasting models.

Our method incorporates the prior knowledge of the storage model and infers the hidden reward that incentivizes the energy storage decisions. This is achieved through a dual-

layer framework, combining a predictive layer with an optimization layer. We have also developed a hybrid loss function for effective model training.

The numerical experiments on synthetic and real-world energy storage data show that our approach achieves the best performance against existing benchmark methods, which shows the effectiveness of our method.

57 **Yilmaz, Elanur**
Associate Research Scientist, Neurology/Taub Institute
"Cross Species Single-cell/nucleus RNA-seq Uncovers the Evolutionarily Conserved Pathological Mechanisms of Vascular Contribution to Alzheimer's Disease"

The latest scientific advancements have revealed previously unidentified genes correlated with the concurrent presence of vascular pathologies and Alzheimer's disease (AD). Yet, the biological functions and mechanisms underlying their contribution to the disease pathology remain to be elucidated. Animal models enabling efficient functional screenings are essential. In pursuit of this aim, we created transgenic adult zebrafish models to investigate the pathological effects of amyloid toxicity. We conducted transcriptome analyses in zebrafish models, integrated with and compared to single nucleus transcriptome datasets from multi-ethnic Alzheimer's disease (AD) cohorts. In this project, we integrated eight single cell dataset of zebrafish model with amyloid toxicity with 24 sex-age matched human AD and control single nucleus transcriptomics data. After filtering out the low-quality cells, we analyzed 177,771 cells distributed in 38 clusters that belongs to 11 different cell types. Following the differentially expressed gene analysis and GO/KEGG pathway analysis, we identified evolutionary conserved changes in VEGF signaling pathway. To investigate the role of VEGF signaling further, we treated zebrafish with the KDRL inhibitors and performed single cell transcriptome analyses. As a result of single cell sequencing of treated fish, we analyzed 22,713 cells in 14 assigned cell types. With this analysis, we hypothesized a previously unidentified crosstalk between brain and vasculature and performed histological and functional analyses. Our studies propose zebrafish as a useful model for transcriptional and functional investigation of the contribution of vascular cells to AD pathology.

58 **Yu, Lexiang**
Postdoctoral Research Scientist, Pathology and Cell Biology
"The Role of IgG in Aging and Metabolic Health: A New Perspective"

Dysfunction of adipose tissue (AT) is a significant hallmark of aging. What drives this in the aging process remains enigmatic. Here we report the accumulation of immunoglobulin G (IgG) antibodies in aged mice, most notably in white adipose tissue (WAT). These IgG depots promote AT dysfunction and metabolic decline. Conversely, caloric restriction (CR) markedly reduces IgG accumulation in WAT, whereas the re-introduction of IgG offsets CR's metabolic benefits. Mechanistically, IgG activates macrophages and induces fibrosis in WAT through the TGF-b/SMAD pathway. Despite this, mice lacking mature B cells are protected from WAT fibrosis and inflammation in aging. However, mice with a conditional knockout of FcRn in macrophages, the receptor

responsible for recycling IgG, prevent WAT accumulation of IgG with aging, and present with improved metabolic health and a prolonged lifespan. Targeting FcRn using antisense oligonucleotides also rejuvenate WAT integrity and metabolic functioning in aged mice. These findings reveal IgG as an unexpected culprit in aging-associated WAT degeneration and metabolic decline, thus providing a new strategy in retaining health during aging.

59 **Zhao, Meng**
Postdoctoral Research Scientist, Biomedical Informatics
"Computational Phenotyping of Kidney Transplantation Using Multiway Models"

Background. The outcomes of kidney transplantation depend on many factors. Discovering sub-phenotypes of patients who had kidney transplantation can help characterize cohorts for treatments planning. Recent advances in unsupervised machine learning on electronic health record (EHR) data have enabled researchers to discover phenotypes without input from domain experts. Our objective in this work is to assess the benefits of an unsupervised approach to model kidney diseases in phenotype discovery.

Methods. In this study, we applied a constrained non-negative tensor-factorization approach to characterize the complexity of kidney transplantation patient cohort based on EHR data. Through tensor factorization, we identified a set of phenotypic topics (i.e., sub-phenotypes) that these patients had different short-term and long-term outcomes after the diagnosis of the first kidney transplantation. Furthermore, we predict the outcome of among the four different results of kidney transplantation (i.e., recover, re-transplant, dialysis, and death) using three different classification algorithms.

Results. From a cohort of 4000 adult individuals who had kidney transplantation, we successfully identified 4 sub-phenotypes using EHR data (368 condition codes and 123 drug codes). We found some phenotypic topics such as diabetes mellitus. Through a downstream application, i.e., the outcome prediction of kidney transplantation, we found markedly different risks of outcome prediction, indicating these topics may capture clinically meaningful sub-phenotypes of kidney transplantation.

Conclusions. The findings of this research demonstrate the promising advantages of applying tensor decomposition techniques in analyzing diseases through EHR data. The outcomes indicate that such methods could aid researchers in identifying sub-phenotypes of complex diseases (e.g., kidney transplantation), which is pivotal for precision medicine studies.

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