IMS Scientific Day 2025

OVERVIEW

Agenda

8:00 – 8:30	**Registration & Breakfast**
8:30 – 9:45	**Alan Wu Poster Competition Session 1**
9:45 – 10:30	**Welcome and Director's Report**
10:30 – 11:30	**Keynote Lecture**
11:30 – 12:45	**Alan Wu Poster Competition Session 2**
12:45 – 2:00	**Lunch Break**
2:00 – 3:00	**Laidlaw Manuscript Competition**
3:00 – 3:15	**Break**
3:15 – 4:15	**Awards Ceremony**
4:15 – 5:00	**Reception**

Poster Locations & Judges

Group	Session & Room		Judges	
A	1	East Common	Angela Mailis	Stephen Juvet
B	1	East Common	Armand Keating	Rohit Mohindra
C	1	East Common	Amit Singnurkar	Alastair Flint
D	1	East Common	David Mikulis	Reinhart Reithmeier
E	1	Music	Kelsey McLaughlin	Pamela Plant
F	1	Music	Theodore Brown	Danielle Bentley
G	1	Music	Sergio Rueda	Robert Vanner
H	1	Music	Amy Boyle	Tom Wright
I	1	Donald Burwash	Anirban Das	Noushin Jafarpisheh
J	1	Donald Burwash	Michael Corrin	Sara Sadat-Afjeh
K	2	East Common	Caleb Browne	Gaspard Montandon
L	2	East Common	Stephen Juvet	Shehryar Saharan
M	2	East Common	Shree Bhalerao	Charlotte Probst
N	2	East Common	Amit Singnurkar	David Mikulis
O	2	Music	Lucas Narciso	Pascal Tyrrell
P	2	Music	Ana Konvalinka	Julia Upton
Q	2	Music	Arun Tiwari	Danielle Bentley
R	2	Music	Richard Swartz	Michael Velec
S	2	Donald Burwash	Shannon Lange	Nicolette Stogios
T	2	Donald Burwash	Yaping Jin	Noushin Jafarpisheh

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ABSTRACTS

A: Neuroscience & Brain Health

A.1: Dynamic changes in cortical thickness with surgical pain relief in trigeminal neuralgia

Student: Emili Adhamidhis, Supervisor: Mojgan Hodaie

Background: Trigeminal neuralgia (TN) is a severe, chronic neuropathic facial pain condition. Although TN can be highly amenable to surgical treatments, ~25% of patients remain in pain or have recurrence of pain following treatment. The mechanisms underlying the effect of surgical treatment in TN remain unclear. Previously, machine learning models identified 13 neuroanatomical regional predictors of surgical response in TN using measures of pre-surgical cortical thickness.

Purpose and Hypothesis: Here, we attempt to further address and understand mechanistic alterations post-surgery in TN by investigating how these previously identified regional predictors of surgical response potentially modify following treatment.

Methods: Retrospective imaging data was acquired from 116 surgically naïve TN patients that underwent Gamma Knife Radiosurgery at Toronto Western Hospital. Patients underwent pre- and post-surgical magnetic resonance imaging (MRI) scans and reported pain intensity levels on a Numerical Rating Scale (NRS) and the Barrow Neurological Institute (BNI) scale at both timepoints. Patients were categorized as either surgical responders ($\geq$ 75% pain relief), partial responders (50-74% pain relief), and non-responders (<50% pain relief). Cortical thickness measures were extracted via FreeSurfer 7.3.2 and statistical analyses were conducted on Python v3.12.1.

Results: 7 regions within the default mode, visual, limbic, and dorsal attention networks had significant ($p < 0.05$) changes in cortical thickness in surgical responders. Post-surgical gray matter changes differed between response groups, with responders having significantly more widespread change than both partial and non-responders. Notably, cortical thickness alterations of the bilateral fusiform gyrus were observed only in the responder groups with > 50% decrease in pain intensity. Morphological changes of the fusiform gyrus were significantly correlated with the degree of pain reduction, highlighting this region as distinctly important to the process of post-surgical pain relief.

Conclusions: Our findings identify key regions that are differentially impacted by chronic neuropathic pain and post-surgical morphological changes that are directly associated with pain relief in TN.

A.2: The causal role of the human posterior thalamus in the control of visual attention

Student: Regina Annirood, Supervisor: Robert Chen

Background: The thalamus has traditionally been considered a relay structure for transmitting information to the cortex without active involvement. However, recent animal studies have challenged this view, demonstrating that thalamic manipulations can affect executive functions. . In the past, it was not feasible to causally study potential roles of the human thalamus in executive functions as traditional non-invasive brain stimulation methods could not target this structure. By using transcranial ultrasound stimulation (TUS), which allows for targeted stimulation of deep brain areas, we tested the hypothesis that the human pulvinar, a posterior thalamic nucleus, actively contributes to the control of visual attention.

Methods: Fifteen healthy participants provided informed consent and completed a visual search task. In this task, participants identified a "T" character among "L" distractors on a screen, with the number of distractors varying across trials (1, 4, 8, 16, or 32). Participants pressed a key to indicate the presence or absence of the "T," with response time and accuracy recorded to assess the impact of distractor count on visual attention and search efficiency.

A control task was included, targeting the globus pallidus internus (GPi), a region associated with response inhibition, using a stop signal task. In this task, participants pressed an arrow key corresponding to the direction of a white arrow displayed on the screen. In some trials, the arrow turned blue, signaling them to halt their action. The time taken to respond to the stop signal, termed the stop-signal reaction time (SSRT), served as a measure of response inhibition.

We used BabelBrain, a Python-based tool, to plan optimal sonication trajectories. This ensured compensation for ultrasound loss through the skull and maintained safe acoustic intensities and thermal levels. The TUS protocol consisted of 120-second sequences of 20-millisecond ultrasound bursts delivered at 5 Hz (theta burst), repeated every 200 milliseconds, targeting either the pulvinar or GPi bilaterally.

Results: Our results demonstrated a double dissociation of effects: TUS of the pulvinar enhanced visual attention, reflected in improved search efficiency, without affecting response inhibition. Conversely, TUS of the globus pallidus internus selectively impaired response inhibition, evidenced by longer SSRTs, while leaving visual attention unaffected.

Conclusion: This dissociation highlights the distinct cognitive functions of the pulvinar and the globus pallidus internus, while establishing a causal link between pulvinar activity and attentional modulation. Moreover, our study demonstrates that TUS has great potential to causally investigate functions of deep brain areas that cannot be targeted by other noninvasive brain stimulation techniques.

A.3: Adjunctive treatment with semaglutide for cognitive dysfunction in the major depressive disorder: Effects of body roundness index on cognitive function (secondary analysis)

Student: Sebastian Badulescu, Supervisor: Rodrigo Mansur

Background: Major Depressive Disorder (MDD) is often co-morbid with cognitive dysfunction. Cognitive function in MDD is a principal determinant of patient-reported health outcomes, independent of concurrent mood symptoms. These cognitive deficits are, among other factors, also linked to metabolic disruption, such as increased insulin resistance. These disruptions are likewise affected by obesity and visceral fat levels. As such, glucagon-like peptide one agonists such as Semaglutide act on these metabolic systems via stimulation of insulin secretion.

Purpose and Hypothesis: A secondary analysis of a clinical study assessing the effects of Semaglutide in treating cognitive dysfunction in MDD. The secondary analysis looks at the impact of the Body Roundness Index (BRI) on cognitive function in MDD. It is expected that the BRI will affect overall cognitive performance.

Methods: This secondary analysis is based on a 16-week randomized, double-blind, placebo-controlled study. Calculated BRI values were derived from height and waist circumference measurements of 72 MDD participants. Cognitive measurements were based on the Trail Making Task A and B (TMT-A/B), the Digit Symbol Substitution Test (DSST), and the Rey Auditory Verbal Learning Test (RAVLT).

Results: The participants' BRI was reduced post-treatment with Semaglutide compared to those on Placebo ($t(51)= 2.526$, $p=0.015$). Additionally, a Linear Mixed Model analysis revealed significant effects of BRI on cognitive function, as measured by performance on the TMTA ($F(1,9.07)=8.681$, $p=0.016$), DSST ($F(1,132.29)=23.524$, $p<0.001$), and the immediate ($F(1,49.16)=7.490$, $p=0.009$) of the RAVLT. However, BRI had insignificant effects on TMTB ($F(1,32.65)=0.997$, $p=0.325$), performance on the proactive interference ($F(1,5.84)=0.091$, $p=0.774$) and delayed recall ($F(1,38.65)=3.312$, $p=0.077$) lists of the RAVLT

Conclusion: BRI's mixed significance (BRI is a more effective metric of visceral adipose tissue than BMI) highlights the different physiological processes encompassing cognitive function. Thus, it emphasizes the role of metabolism in cognitive domains such as processing speed and attentional capacity.

A.4: Status dystonicus is a distinct state characterized by pallidal beta-band activity

Student: Arjun Balachandar, Supervisor: Alfonso Fasano

Background: Status dystonicus (SD) is a poorly understood neurological emergency requiring urgent interventions, including globus pallidus interna (GPi) deep brain stimulation (DBS). Sensing-capable DBS electrodes provide an opportunity to study SD pathophysiology. Despite increasing use of pallidal DBS, oscillatory & non-oscillatory electrophysiological signatures of SD remain unknown.

Purpose: Identify intracranial neural biomarkers of SD from a rare cohort of children, critical since children at risk often have chronic baseline dystonia difficult to differentiate from SD.

Hypothesis: Distinct local field potential (LFP) signatures characterize SD from non-SD dystonia.

Methods: Ten patients with SD (Hospital for Sick Children, Canada) were implanted with Medtronic Percept™ GPi DBS (age: 7.8±3.6). LFPs were recorded longitudinally during SD, recovery and relapse (range: 11-1155 days) and Power Spectral Densities (PSDs) calculated (Welch-method). Analysis of oscillatory and aperiodic activity was performed (fitting-oscillations/one-over-f). Band-limited power (Theta: 3-7Hz; Alpha: 7-12.5Hz, Beta: 12.5-30Hz) was calculated. Generalized linear mixed effects models assessed relations between LFP metrics and clinical scales, including Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS) and Pediatric Quality of Life Score (PedsQL). Circadian LFP dynamics were assessed in one participant with narrowband beta-band recordings over months.

Results: During SD, the periodic peak in the beta-band ($p=0.007$) and beta-band burst amplitude ($p<0.001$) increased. Relapsed SD was characterized by return of excessive beta signatures. Beta-specific LFP power was significantly associated worse quality-of-life scores (PedsQL, $p=0.03$, $R^2=0.695$). Circadian beta-band periodicity was present, with significantly increased power across daytime ($p<0.001$) and nighttime ($p<0.001$) during SD.

Conclusions: SD is a distinct state with important implications for dystonia pathophysiology, tracking dystonia-states from intracranial activity and potential adaptive DBS treatments.

A.5: Biomarkers of longevity in Dravet Syndrome: A scoping review on human and animal models

Student: Ilakkiah Chandran, Supervisor: Danielle Andrade

Background: Dravet Syndrome (DS) is a rare and treatment-resistant epilepsy. Aside from the many comorbidities patients with DS experience, sudden unexpected death in epilepsy (SUDEP), premature mortality, and premature aging have been highlighted at increased rates among this population. Despite this, there continues to be a lack of information in understanding whether there are biomarkers that can be used to understand DS patients' longevity.

Purpose: This scoping review aims to analyze and summarize the existing literature on DS biomarkers among patients and animal models of DS to understand their impact on longevity.

Methods: To conduct a comprehensive search of the literature, a search strategy was developed combining keywords and Medical Subject Headings related to Dravet Syndrome, biomarkers and longevity. The strategy was run in 9 databases, and results were exported to Covidence. Eligibility was screened by three independent reviewers and two reviewers completed data extraction.

Results & Implications: A total of 3321 studies were exported. After deduplication, 1411 studies' titles and abstracts were screened. 338 studies' full texts were assessed for eligibility. 62 articles were included in this scoping review, 23 of which focus on human participants. Data analysis is ongoing.

Once this review is complete, it will inform future research on DS to focus on evaluating biomarkers among patients and their relation to physical manifestations of premature aging (i.e., motor function and Parkinsonian manifestations). The study will also emphasize the necessity include investigations of the identified biomarkers in clinical evaluations to support the quality of life of patients.

A.6: Exploring the neurobiology of irritability and suicidality in major depressive disorder: A pilot fMRI study

Student: Aaima Cheema, Supervisor: Katharine Dunlop

Background: Suicide is a leading cause of death in North America. In major depressive disorder (MDD), understanding the biological link between irritability and suicidal thoughts/behaviors (STB) may help identify risk factors. Both irritability and STB engage similar brain circuits involved in social cognition, emotion, and executive function. However, no neuroimaging studies have examined their relationship in MDD. This study aims to identify differences in the neural correlates of irritability in MDD individuals with a suicide attempt, relative to those with no attempt history, and healthy controls.

Methods: This pilot study included 18 participants (ages 18-65, 13 female): ten healthy controls (HC), eight MDD participants with STB. Participants completed two task-based fMRI paradigms: one assessing negative affect following social exclusion and the second evaluating retaliation toward excluders. Two first-level event-related general linear models (GLM) will model task-related activity for each task. We will use GLMs, controlling age, sex, and depression severity, to test for between-group differences.

Results: Across all groups, social exclusion activated the anterior cingulate cortex (ACC), precuneus, and posterior cingulate cortex ($p<0.05$). Compared to HC, irritability in MDD was linked to increased ACC and dorsomedial prefrontal cortex (DMPFC) activity. During retaliation, irritability in MDD negatively correlated with ACC and DMPFC activity. In contrast, forgiveness of excluders was positively correlated with dorsolateral prefrontal cortex (DLPFC) activity ($p<0.05$).

Conclusion: This study identifies prefrontal activity in MDD is linked to irritability. These findings provide the first neurobiological insights into the relationship between irritability and suicidality in MDD. The identified brain targets could lead to the development of innovative neurostimulatory treatments for STBs in individuals with irritability.

Keywords: Suicide, Irritability, Neurobiology, Functional Magnetic Resonance Imaging, Major Depressive Disorder

A.7: Assessing the effect of cognitive remediation combined with transcranial direct current stimulation on brain structure in older adults at risk for Alzheimer's disease

Student: Yihan (Cathlyn) Chen, Supervisor: Aristotle Voineskos

Background: Older adults with remitted major depressive disorder (rMDD) or mild cognitive impairment (MCI) are at elevated risk for Alzheimer's disease (AD). A recent clinical trial in these populations demonstrated that combining cognitive remediation (CR) with transcranial direct current stimulation (tDCS) improved cognition (executive function and verbal memory) and may protect against AD. This study aims to investigate the neural mechanisms of this intervention.

Purpose: The objective is to compare changes before and after treatment between groups exposed to CR+tDCS vs. sham CR+sham tDCS in **1)** Grey matter morphology measured by cortical thickness, surface area, and subcortical volume in selected regions of interest. **2)** White matter microstructural integrity measured by fractional anisotropy and mean diffusivity, both average and in selected tracts.

Hypothesis: It is hypothesized that participants receiving active CR+tDCS will show greater improvements in grey and white matter structure compared to those receiving sham treatment. Specifically, treatment effects are expected to be most pronounced in frontal and temporal regions, reflecting improvements in executive function and verbal memory.

Methods: 375 participants over 60 were randomized to active CR+tDCS or sham treatment. 227 completed magnetic resonance imaging (MRI) scans before and after treatment, and 181 (96 MCI, 85 rMDD) were included in the analysis following quality control. MRI measures of grey matter structure (cortical thickness, surface area, subcortical volume) and white matter microstructure (fractional anisotropy, mean diffusivity) were assessed. Linear models tested the effect of treatment on changes in MRI outcomes accounting for covariates, including age, sex, education, APOE e4 status, diagnosis, and the respective MRI measures at baseline.

Results: Active treatment had no main effect on regional MRI changes. However, Diagnosis significantly moderated changes in several MRI measures, with the strongest effect in the caudal middle frontal surface area ($p=0.038$ after FDR correction), where individuals with rMDD showed greater brain improvement. Baseline MRI measures also moderated changes in brain structure, notably baseline cingulum mean diffusivity ($p=0.063$).

Conclusion: While the combined intervention did not affect brain structure compared to sham treatment, it had differential effects based on diagnosis and baseline brain structure. Since the treatment may have a greater impact on the brain in certain groups, these results highlight the potential for personalized interventions targeting individuals most likely to benefit.

A.8: Investigating the genetics of depression and anxiety in a multi-ancestral cohort of children and adolescents with systemic lupus erythematosus

Student: Indrani Das, Supervisor: Linda Hiraki

Background: Patients with childhood-onset systemic lupus erythematosus (cSLE) have a higher prevalence of depression and anxiety compared to healthy peers. Genome-wide association studies (GWAS) have identified >100 genetic risk loci for each of depression, anxiety and SLE.

Purpose/Hypothesis: We aim to test the association between genetic risk variants for 1) SLE (HLA and non-HLA) and 2) MDD with depression and anxiety, in children and adolescents with SLE. We hypothesize that these risk variants are associated with depression and anxiety in this population.

Methods: We included patients followed in a tertiary care Lupus clinic from January 1, 2000, to December 31, 2023. All patients met ≥4 ACR and/or SLICC criteria for SLE with data collected in a dedicated lupus database. Patients were genotyped on an Illumina multiethnic array. Ungenotyped single nucleotide polymorphisms (SNPs) were imputed using TopMed as a referent. Ancestry was genetically inferred using principal components (PCs) and ADMIXTURE. We calculated additive, weighted PRSs for SLE (HLA and non-HLA) and MDD using risk SNPs from the largest GWAS available. We identified patients with depression and anxiety based on a diagnosis and/or persistent symptoms ≥ 2 months, before or after SLE diagnosis. We tested the association between each PRS and 1) depression only, 2) anxiety only, 3) depression and anxiety, 4) depression and/or anxiety in univariate and multivariable logistic regression models, adjusted for sex and 5 PCs (P<0.0.017). We conducted two sensitivity analyses focused on 1) only patients with diagnosed depression and anxiety, and 2) adjusting for neuropsychiatric lupus (NPSLE).

Results: Our study included 488 patients, 84% were female, with a median age of SLE diagnosis of 14 years (IQR: 12-16). Most patients were of European (29%) and East Asian (27%) ancestry. Common SLE clinical features included arthritis (68%), lupus nephritis (39%) and NPSLE (21%). 96 (20%) patients had a depression and/or anxiety diagnosis: 28 (6%) with depression only, 25 (5%) with anxiety only, and 43 (9%) with both depression and anxiety. 181 (37%) patients had depression and/or anxiety persistent symptoms: 138 (28%) with depression only, 4 (1%) with anxiety only, and 39 (8%) with both depression and anxiety. We did not observe a significant association between the PRSs and depression or anxiety. Sensitivity analyses demonstrated similar associations. NPSLE was significantly associated with depression diagnosis (OR 3.89, 95% CI 2.26-6.68; P<0.001).

Conclusions: In a multi-ancestral cohort of patients with cSLE, we did not observe a significant association between genetic loci for SLE and MDD and depression or anxiety. Future work will examine the genetic variants for anxiety.

B: Neuroscience & Brain Health

B.1: Investigating microstate metrics in mild cognitive impairment and remitted major depressive disorder: A PACt-MD analysis

Student: Sushmit Das, Supervisor: Andreea Diaconescu

Background: Electroencephalogram (EEG) microstates can be used to assess brain networks in individuals with mild cognitive impairment (MCI) or remitted major depressive disorder (rMDD) – two high-risk conditions for dementia.

Purpose: Previous studies are limited by small sample sizes and insufficient focus on cognition.

Hypothesis: Using large and cognitively well-characterized samples, and based on previous findings from a meta-analysis, we hypothesized that microstate-B duration and microstate-D occurrence are increased both in MCI and rMDD, compared to older healthy controls (HC).

Methods: We used data collected as part of the PACt-MD study. Resting-state EEG were analyzed using k-means clustering. We also investigated the relationships between microstates and cognition, assessed using a comprehensive cognitive battery. ANCOVA and regression analyses examined cognition, controlling for age, sex, and education.

Results: Comparing participants with HC (n=46; mean age[SD] years=69.5[5.3]), MCI (n=108; 72.8[7.4]), or MDD (n=50; 70.4[4.8]), no significant differences were observed in microstate-B duration in milliseconds(ms) (HC vs. MCI) or microstate-D occurrence (HC vs. MDD). Neither microstate parameters were significantly associated with cognition.

However, in post-hoc analyses, HC females had longer microstate-C durations (ms) than HC males (93.40[1.28] vs. 82.68[1.52]; $t(44)=-2.50$, $p = 0.016$); by contrast, males with rMDD had longer microstate-C durations than females with rMDD (106.03 [1.90] vs. 87.69 [1.49]; $t(48)=3.616$, $p<0.001$). A confirmatory analysis in an independent sample of 28 HC participants and 31 participants with MCI showed similar sex differences.

Conclusions: Specific microstate metrics do not reliably indicate cognitive deficits in MCI or rMDD. Sex differences in rMDD vs. HC vs. MCI groups need further investigation.

B.2: Resting-state neural oscillatory activity in concussion: Investigating symptomatic and subclinical states using magnetoencephalography

Student: Eleftheria Daskalakis, Supervisor: Ben Dunkley

Background: Concussion, is a form of mild traumatic brain injury, which affects millions globally every year. For many, concussion symptoms resolve within a month of the injury. However, 10–20% of individuals experience persistent symptoms that significantly impair daily functioning. The presentation of these persistent concussion symptoms is also idiosyncratic and heterogeneous, and our understanding of the mechanisms that underlie persistent symptoms has yet to be determined. Elucidating these mechanisms, therefore is crucial for improving prognosis, refining diagnostic criteria, and developing targeted interventions.

Magnetoencephalography (MEG) represents a neurophysiological tool that is ideally suited to investigate concussion-related neurophysiological alterations due to its high temporal resolution and sensitivity to subtle functional disruptions. MEG is particularly effective in detecting subtle functional brain alterations that may not be apparent using structural or other functional imaging techniques (e.g., fMRI). It is also an ideal method for identifying robust differences between asymptomatic and symptomatic individuals following concussion.

Purpose and Hypothesis: The purpose of this study was to examine the neurophysiological underpinnings of concussion symptomatology using MEG. We hypothesized that individuals with resolved overt symptoms will exhibit neural activity patterns resembling those of uninjured controls. In contrast, symptomatic individuals will demonstrate distinct deviations, including increased delta and theta activity, reduced beta activity, and altered gamma activity.

Methods: Individuals with a history of concussion were classified into subclinical and symptomatic subgroups using k-means clustering on SCAT2 symptom profiles. MEG recordings were analyzed to assess power spectral density across frequency bands, covarying for age. Both periodic (delta, theta, alpha, beta, gamma) and aperiodic (exponent, offset) components of neural activity were examined, with multiple comparison corrections applied for statistical rigour.

Results: Clustering analysis delineated four distinct clusters. One cluster, characterized by markedly attenuated symptom severity, was designated as "subclinical," whereas the remaining three clusters—each exhibiting varying degrees of symptomatology—were collectively classified as ‘symptomatic’. MEG analyses revealed significant group differences ($p < 0.05$). Compared to the symptomatic group, the subclinical group exhibited **increased theta and delta activity, decreased beta activity, and reduced gamma activity**. Aperiodic signal analysis showed a **higher whole-brain exponent and offset** in the subclinical group, indicating greater inhibitory activity. Regionally, the subclinical group also displayed a **higher frontal exponent**, further distinguishing neurophysiological patterns between groups.

Conclusion and Significance: These findings challenge the notion that concussion recovery simply restores pre-injury neural function. The outcome's directionality indicates that recovery involves distinct neurophysiological adaptations rather than a simple return to baseline. This underscores the need for further research to explore the recovery mechanisms the brain employs to mitigate concussion symptoms and how these adaptations influence long-term outcomes. Understanding these processes could refine clinical assessments and inform more effective rehabilitation strategies for individuals recovering from concussions.

B.3: Imaging-transcriptomic associations reveal region-specific gene-structure relationships

Student: Thomas DeLong, Supervisors: Shreejoy Tripathy

Background: Previous imaging transcriptomics studies often relied on unmatched data or single-region RNA to link brain structure and gene expression. Newly available datasets with structural MRI (sMRI) and multiple RNA samples per subject enable direct analyses of transcriptomic variation in relation to brain structure.

Purpose: This study investigates how transcriptomic variation across different brain regions corresponds to MRI-derived structural features, addressing whether gene–MRI associations are region-specific.

Hypothesis: Gene-MRI associations are highly region specific and vary considerably based on the brain region where RNA is sampled from.

Methods: We analyzed ROSMAP data from individuals with ante-mortem MRI and post-mortem bulk RNA-seq in five brain regions, comprising 479 samples from 148 individuals. A subset of 96 individuals had RNA-seq from both the temporal and frontal cortex, enabling direct comparisons. MRI features were processed in FreeSurfer (Schaefer parcellation) with site-related batch correction. Linear models assessed gene–MRI associations, adjusting for time between MRI acquisition and death. Rank-biased overlap (RBO) was used to compare gene associations across regions.

Results: Gene–MRI associations varied markedly by RNA-seq region. In the posterior cingulate cortex, 32 genes were associated with average cortical thickness, whereas 5,043 genes in the caudate nucleus showed associations (FDR<0.05). Notably, 2,153 caudate genes correlated with thickness in the right frontal eye fields. Direct parcel-wise comparisons between frontal and temporal cortex showed minimal overlap (RBO≈0).

Conclusions: Transcriptomic correlates of structural MRI measures are highly region-specific, with minimal cross-region overlap. These findings suggest that single-region or unmatched approaches may overlook key heterogeneity in gene–structure relationships, emphasizing the need for region-specific sampling and analysis strategies.

B.4: Executive function in autism during middle and older adulthood

Student: Azra Delpak, Supervisor: Evdokia Anagnostou

Background: Executive function (EF) refers to cognitive processes such as working memory, cognitive flexibility and inhibitory control, which are essential for goal-directed behavior. EF impairments are not well-documented in autistic adults and research on how these functions change with aging remains limited. Aging is generally linked to EF decline, but it is unclear whether autistic adults experience accelerated, parallel, or distinct cognitive aging compared to neurotypical individuals. Some studies suggest increased vulnerability to neurodegenerative conditions, while others indicate stability or compensatory mechanisms. Previous research has reported mixed results related to differences in EF decline between autistic and neurotypical adults, though factors such as late diagnosis, education, and comorbidities may influence outcomes.

Purpose and Hypothesis: The purpose of this study is to identify, appraise, and synthesize existing evidence on differences in executive function (EF) domains—working memory, set-shifting, and response inhibition—between autistic adults aged 40 years and older and age-matched neurotypical adults. While aging is generally associated with EF decline, how cognitive aging manifests in autism remains unclear. This study aims to compare EF performance between autistic and neurotypical adults to determine whether autistic adults exhibit greater impairments in these domains. We hypothesize that autistic adults aged 40 and older will show greater EF difficulties, particularly in set-shifting, inhibition, and working memory, compared to neurotypical adults.

Methods: A systematic review will be conducted following PRISMA guidelines. Peer-reviewed empirical studies published from 2015 onward will be identified through systematic searches in the following databases MEDLINE, EMBASE, PsycINFO, and Web of Science. Inclusion criteria require studies to include participants aged 40 years and older diagnosed with autism spectrum disorder (ASD) and assess EF domains (working memory, set-shifting, response inhibition) using standardized or experimental neuropsychological measures. Studies with a broader age range will be included if they contain at least 20 autistic participants aged 40 and older. Eligible study designs include cohort, case-control, and cross-sectional studies. Data extraction will focus on EF outcomes and group comparisons. Findings will be synthesized to evaluate patterns of EF performance in aging autistic adults compared to neurotypical individuals.

Results: The protocol has been completed and submitted to PROSPERO. Search strategy has been finalized. This study is currently ongoing, and updated results will be presented during the Alan Wu Day presentation.

B.5: Genetic modulation of sleep and its role in ADHD and disruptive behaviors: A multimodal longitudinal study

Student: Sohom Dey, Supervisor: James Kennedy

Background: ADHD and Disruptive Behavior Disorders (DBD) are highly heritable conditions, yet environmental factors like sleep play a crucial role in their onset and progression. While research has linked sleep problems to ADHD and DBD, the extent to which they mediate or moderate genetic risk over time remains unclear. Sex-specific pathways linking genetic risk, sleep disturbances, and symptom progression remain poorly understood, warranting further longitudinal investigation into their distinct developmental trajectories.

Purpose and Hypothesis: This study investigates how polygenic risk (PRS) for ADHD and aggression interacts with sleep disturbances to influence symptom severity and progression, using a longitudinal, sex-stratified approach. We hypothesize that PRS for ADHD and aggression are associated with greater ADHD and DBD severity, with sleep disturbances both mediating and moderating these effects differently across sexes.

Methods: Data from 4,888 unrelated European adolescents in the ABCD Study were analyzed. ADHD and DBD severity were assessed via the Child Behavior Checklist, and sleep disturbances (SDS) were parent-reported. PRS for ADHD and aggression were calculated using PRS-CS. Linear mixed-effects models tested PRS, sleep, and symptom severity associations. Latent growth curve modeling examined longitudinal symptom trajectories, integrating mediation and moderation.

Results: PRS for ADHD and aggression were strongly associated with symptom severity, predicting baseline severity but not symptom progression. SDS had a greater baseline impact in males than females for ADHD (β = 3.808 vs. 1.426) and DBD (β = 3.156 vs. 1.456). Longitudinally, SDS contributed more to DBD progression in males than females (β = 6.454 vs. 4.378), while ADHD progression was affected only in males (β = 4.028). Mediation analyses showed that SDS explained more genetic risk for ADHD in females (31.6%) than males (26.9%), while for DBD, mediation was stronger in males (25.4%) than females (22.2%). Moderation analyses revealed that SDS amplified genetic effect on ADHD in females while its effect on DBD was similar across sexes.

Conclusions: Our findings demonstrate that sleep disturbances are a critical mechanism linking genetic risk to ADHD and DBD, with distinct sex-specific patterns. These results highlight sleep as both a mediator and moderator of genetic risk, underscoring the need for sleep-targeted interventions to mitigate genetic vulnerabilities in ADHD and DBD. Future research should explore neurobiological and environmental mechanisms underlying these sex differences to inform personalized treatment approaches.

B.8: Sex differences in the neuropsychiatric sequelae of multiple sclerosis

Student: David Freedman, Supervisor: Anthony Feinstein

Background: Sex differences exist in vulnerability to multiple sclerosis (MS) and disease progression. Although depression, anxiety, fatigue, perceived cognitive deficits, and cognitive dysfunction vary by sex in the general population, there is mixed evidence for these differences in people with MS (pwMS).

Purpose and Hypotheses: The purpose of this study is to evaluate for sex differences in the neuropsychiatric sequelae of MS. In pwMS, we anticipated that females would experience greater anxiety, fatigue, and subjective cognitive concerns compared to males, but that depressive symptoms would not differ by sex. Regarding cognition, we hypothesized that females would have better performance than males on tests of learning/memory, while males would outperform females on tests of visuospatial processing and working memory.

Methods: A consecutive sample of 1,530 pwMS (diagnosed per the McDonald criteria) aged 18-65 routinely completed neuropsychological testing at a tertiary neuropsychiatry clinic in Toronto, Canada from 2005 to 2025. Demographic data included age, education, Expanded Disability Status Scale (EDSS) scores, disease duration, and disease subtype. Neuropsychiatric measures included the Hospital Anxiety and Depression sub-scales for anxiety (HADS-A) and depression (HADS-D), the Modified Fatigue Impact Scale (MFIS), the Perceived Deficits Questionnaire (PDQ) for subjective cognitive concerns, and the Minimal Assessment of Cognitive Function in MS (MACFIMS) cognitive battery. These measures were previously validated in pwMS. Linear regression models predicted neuropsychiatric raw scores from sex, adjusted for all of the above demographics (p<.01).

Results: Seventy-three percent of participants were female. Mean age was 43.2 years (SD=10.6), mean education was 15.8 years (SD=3.0), median EDSS was 2.0 (IQR=1.5–3.5), mean disease duration was 9.7 years (SD=8.4), and 83.3% had relapsing MS (RMS). Females had lower EDSS scores, longer disease duration and were more likely to have RMS than males, all p<.01. Controlling for demographics, females scored higher than males on MFIS, PDQ, tests of verbal learning and memory (California Verbal Learning Test – 2nd edition) and visuospatial learning (Brief Visuospatial Memory Test - Revised), but worse on tests of visuospatial processing (Judgment of Line Orientation) and working memory (Paced Auditory Serial Addition Test), all p<.01. No significant sex differences were found in HADS-A, HADS-D, or other MACFIMS scores.

Conclusions: In pwMS, females, on average, experience more fatigue and subjective cognitive concerns compared to males, but outperform males in learning and verbal memory. Males perform better than females in visuospatial processing and working memory. Symptoms of anxiety and depression do not differ by sex. Limitations include a sample bias toward relapsing illness and lack of data on hormonal changes across the lifespan. While sex differences in fatigue and cognition align with general population trends, the null findings for anxiety and depression in MS do not, meriting future exploration.

C: Neuroscience & Brain Health

C.1: Examining the role of IL-1R antagonism in treating postpartum depression using a rodent model

Student: Romina Garcia de leon, Supervisors: Liisa Galea

Background: Depression risk is highest during the postpartum [postpartum depression (PPD). Selective serotonin reuptake inhibitors (SSRIs) are often prescribed for PPD, however, only 3.2% of females with PPD achieve remission with SSRIs. In our preclinical model of PPD, we administer high corticosterone (CORT) during the postpartum. We found increased levels of the proinflammatory cytokine IL-1β in the hippocampus was commensurate with reduced SSRI efficacy, indicating this may be an important target to boost SSRI efficacy. Our central hypothesis is that antidepressant efficacy in the postpartum is mediated by inflammatory signalling.

Methods: High CORT was administered during the postpartum period to dams starting on postpartum day 2 along with fluoxetine (FLX) and/or anakinra (KIN), an IL-1R antagonist. FLX efficacy was measured using the forced swim test (FST), and maternal care observations. All dams were euthanized 23 days later to examine inflammation and neuroplasticity in the hippocampus and frontal cortex.

Results: Dams treated with KIN (with or without FLX) failed to rescue passive coping behaviours in the FST. However, FLX and KIN together were able to rescue reductions in neuroplasticity as noted in hippocampal perineuronal net (PNN) expression and doublecortin (DCX+ cells) expression. Additionally, in CORT treated dams, FLX increased a Th_1/Th_2 inflammatory ratio in the dorsal hippocampus, but FLX+KIN treated dams had a reduction in Th_1/Th_2 ratio. Current analyses are in progress to quantify PNNs and Th_1/Th_2 ratio in the frontal cortex, alongside postsynaptic density-95 (PSD-95) in both hippocampal and frontal cortex tissue. Lastly, we will quantify the percentage of phagocytic microglia (Iba1+/CD68+) in the hippocampus and frontal cortex.

Conclusions: These findings indicate that IL-1β may serve as a potential target for increasing antidepressant efficacy in people with PPD

C.2: Microglia-derived TMEM119$^+$ extracellular vesicles in plasma are potential biomarkers of HMGB1-mediated neuroinflammation secondary to necrotizing enterocolitis

Student: Miguel Garcia, Supervisors: Augusto Zani

Background: Necrotizing enterocolitis (NEC) is a devastating neonatal disease with a mortality rate of 20-50% and affects infants of primarily non-Hispanic Black and Hispanic descent. NEC causes severe intestinal injury and necrosis, leading to sepsis and death. Among the numerous long-term gastrointestinal complications incurred by NEC, approximately 40% of survivors experience neurodevelopmental impairment, with worse outcomes for surgical NEC survivors. Prior literature has demonstrated HMGB1, a nonhistone nuclear protein, as driving NEC-induced neuroinflammation in a TLR4-dependent manner. Enterocyte apoptosis via NEC leads to the release of HMGB1, which crosses the blood-brain barrier (BBB) and interacts with TLR4 on resident microglia, leading to their activation. Therefore, further research on biomarkers of NEC-mediated neuroinflammation is warranted. Extracellular vesicles (EVs) are membrane-bound nanoparticles that can cross the BBB and have gained interest as potential biomarkers of neurodegenerative diseases. EVs can be sourced from a variety of biofluids like blood and cerebrospinal fluid, and contain bioactive cargo such as miRNAs, proteins and lipids. Notably, prior literature has demonstrated cerebrospinal fluid-derived EVs as potential biomarkers for conditions such as Alzheimer's disease and Parkinson's disease. As microglia play a key role in NEC-induced neuroinflammation, the EVs they release may therefore serve as promising biomarkers.

Purpose and Hypothesis: This study aims to find biomarkers of NEC-induced neuroinflammation in accessible biofluids, which will help to facilitate earlier treatment interventions, parental counseling, and new therapeutic strategies. Therefore, microglia-derived TMEM119$^+$ EVs sourced from peripheral blood plasma may serve as biomarkers of HMGB1-mediated neuroinflammation secondary to NEC.

Methods: Following ethical approval (AUP#58119), 5-day old C57BL/6 mice were separated from their mothers to avoid breastfeeding and were subjected to a 4-day NEC induction protocol consisting of oral administration of lipopolysaccharide, hypoxia, and hyperosmolar formula. Control mice were not removed from their mothers nor subjected to the NEC induction protocol. At day 9, 3 control and 3 NEC mice were sacrificed and had blood collected via cardiac puncture for further analysis. Bulk EVs from plasma were obtained via size-exclusion chromatography, after which TMEM119$^+$ (a microglia surface marker) EVs were enriched via immunocapture. Canonical EV markers and inflammatory markers from bulk and TMEM119$^+$ EVs were assayed via western blot to confirm the presence of EVs. EV size was determined via nanoparticle tracking analysis (NTA).

Results: Compared to control mice, TMEM119$^+$ plasma EVs from NEC mice contained significantly greater levels of NLRP3 ($p=0.003963$). No significant differences in size between bulk EVs (control = 179.80 +/- 7.99nm, NEC = 157.60 +/- 5.89nm) nor TMEM119$^+$ EVs (control = 185.67 +/- 11.41, NEC = 173.03 +/- 12.41nm) were observed.

Conclusions: TMEM119$^+$ microglia EVs sourced from plasma show promise as biomarkers of NEC-induced neuroinflammation. Further studies will focus on further optimizing the immunocapture protocol to identify further microglia-specific EV subsets.

C.3: Characterizing sex differences in functional connectivity during chronic stress-induced negative cognitive bias

Student: Kanak Gupta, Supervisor: Liisa Galea

Background: Major Depressive Disorder (MDD) affects 20% of the population and affects females at twice the rate as males. MDD is characterized by several symptoms including cognitive symptoms, such as negative cognitive bias (NCB). NCB is the increased perception of ambiguous situations as negative. Changes in network connectivity between limbic system regions, including the hippocampus, prefrontal cortex, amygdala, and nucleus accumbens, are implicated in MDD and can predict negative cognitive bias in MDD.

Purpose and Hypotheses: Here we examined possible sex differences in activation patterns and the functional connections within these regions in an animal model. We hypothesize that 1) activation patterns and relationship with NCB will differ by region and sex, 2) functional connectivity patterns in response to CUS-induced negative cognitive bias will differ by sex.

Methods: Male and female Sprague-Dawley rats underwent either 21 days of chronic unpredictable stress (CUS) to induce a depressive-like endophenotype or no CUS. Rats then underwent a cognitive bias task in which, after learning to discriminate between shocked context and a non-shocked context, they were exposed to an ambiguous context (with half the features of the shock vs. no shock context) and freezing behaviors were recorded. Activated neurons were visualised using an immunofluorescent stain for immediate early gene (IEG) c-Fos protein, which is transcribed rapidly in response to stimuli, across 19 limbic regions.

Results: Preliminary data suggests CUS lower activation in the dorsal and ventral hippocampus in males, whereas greater activation is seen in females. Further analysis is underway to study functional connections between the limbic regions.

C.4: Cortical thickness moderates the cogntive outcomes of tDCS and cognitive remediation in older adults wth remitted major depressive disorder or mild cognitive impairment – An analysis of the PACt-MD randomized controlled trial

Student: Natalie Ho, Supervisor: Benoit Mulsant

Background: Cognitive remediation (CR) combined with transcranial direct current stimulation (tDCS) is effective in reducing cognitive decline in at-risk patients with remitted Major Depressive Disorder (rMDD) or Mild Cognitive Impairment (MCI).

Purpose and Hypothesis: We aimed to examine the moderating effects of baseline brain structure magnetic resonance imaging (MRI) measures on the impact of CR+tDCS on longitudinal cognitive outcomes and the effect of participant characteristics on this relationship.

Methods: We analyzed data from the Prevention of Alzheimer's dementia with CR plus tDCS in MCI and Depression (PACt-MD) randomized controlled trial in which 375 participants received CR+tDCS or sham CR+sham tDCS. In 246 participants (age: 71.9±6.2; 152 women) with a baseline MRI scan, we assessed the moderating effect of overall cortical thickness, fractional anisotropy (FA), and cortical thickness in an a-priori composite region of interest (ROI), on changes in global cognition, executive function, or verbal memory.

Results: There were moderating effects of overall cortical thickness on the decline in global cognition (X^2=10.43, df=3, p=0.015) and of ROI cortical thickness on the decline in global cognition (X^2=29.05, df=3, p< 0.001) and executive function (X^2=11.57, df=3, p=0.009), and on change in verbal memory (X^2=16.08, df=3, p=0.001). The difference in the decline in global cognition with active vs. sham treatment was two to three times larger after three years in those with higher overall or ROI cortical thickness than in those with lower overall or ROI cortical thickness. Similar results were observed with executive function or verbal memory. There were no moderating effects of FA.

Conclusion: Future work should confirm that global and regional cortical thickness can be used to select older adults at risk for dementia who are the most likely to benefit from CR+tDCS.

C.5: Chemical chaperones for the prevention of antipsychotic-induced impairments in glucose metabolism

Student: Bailey Humber, Supervisor: Margaret Hahn

Background: Antipsychotic medications increase the risk of developing type 2 diabetes by disrupting glucose metabolism in patients with schizophrenia. Olanzapine (OLA) is an antipsychotic known to impair the ability of insulin to suppress endogenous glucose production (EGP). This impairment is also associated with endoplasmic reticulum (ER) stress and disrupted insulin signaling in the hypothalamus. Chemical chaperones such as sodium 4-phenylbutyric acid (PBA) act as ER stress inhibitors and have been shown to improve insulin sensitivity.

Purpose and Hypothesis: The objectives of this project are to examine if OLA's acute inhibition of central insulin action can be reversed via the co-administration of peripheral chemical chaperones, and if this effect occurs via the reversal of hypothalamic ER stress.

Methods: Pancreatic euglycemic clamps, the gold standard technique to assess in vivo glucose metabolism, were performed in male Sprague Dawley rats. Cannulae were implanted for intracerebroventricular (ICV) insulin administration, and jugular/carotid cannulations allowed infusions and blood sampling. This study was conducted with a 2 x 2 x 2 design, rats received ICV insulin or vehicle, subcutaneous OLA or vehicle, and intravenous PBA or vehicle. Glucose infusion rates were used to assess insulin sensitivity. Hypothalamic tissues were collected for ER stress marker analysis.

Results: ICV insulin increased glucose infusion rates, indicating improved insulin sensitivity (vehicle-vehicle-vehicle: 3.51 SE = 1.32, insulin-vehicle-vehicle: 9.85 SE = 0.82; $p < 0.0001$). OLA abolished this effect (insulin-OLA-vehicle: 3.40 SE = 0.75; $p < 0.0001$). When PBA was added insulin action was not restored (insulin-OLA-PBA: 3.87 SE = 1.52; $p > 0.1$), suggesting it does not counteract OLA's effects. No significant changes were observed in any of the other groups.

Conclusions: This study replicated the finding that OLA suppresses the effects of ICV insulin on glucose metabolism. Additionally, PBA did not alleviate OLA-induced impairments in insulin sensitivity. Future studies could explore extended dosing of chemical chaperones in conjunction with antipsychotic administration.

C.6: Investigating the brain endocannabinoid system in obsessive-compulsive disorder

Student: Hanan Idd, Supervisor: Stefan Kloiber

Background: Many individuals with obsessive-compulsive disorder (OCD) do not respond to current treatments, highlighting the need for new interventions. Evidence from preclinical and initial clinical research indicates a potential role of the endocannabinoid system (ECS) in the pathophysiology of OCD. However, relatively little is known about brain ECS activity in individuals with OCD.

Purpose and Hypothesis: This study will use Positron Emission Tomography (PET) imaging with the radioligand [^{11}C]CURB to measure brain fatty acid amide hydrolase (FAAH) levels in individuals with OCD and compare this to healthy controls (HCs). We hypothesize that brain FAAH levels will be higher in individuals with OCD compared to HCs in the whole brain and cortical and subcortical regions related to OCD.

Methods: This study aims to recruit 30 participants aged 18 to 50 years, meeting DSM-5 criteria for OCD. Participants will complete Magnetic Resonance Imaging (MRI) and PET imaging. Blood samples will be collected for FAAH genotyping. To compare brain FAAH levels between the OCD and HC groups, repeated measures ANCOVA will be used with group as a between subject factor, 10 regions of interest (ROIs) as a within-subject factor and FAAH genetic variability (C385A) as a covariate.

Conclusion: This project will be the first in-vivo study directly investigating brain FAAH activity in individuals with OCD. Findings from this study will provide important insights in our understanding of OCD pathophysiology and could inform development of ECS-targeted therapeutics in OCD.

C.7: Imaging monoacylglycerol lipase: Positron emission tomography study with [^{18}F]MAGL-2102

Student: Bertina Jebanesan, Supervisor: Isabelle Boileau

Introduction: Monoacylglycerol lipase (MAGL) plays a critical role in the endocannabinoid system by metabolizing 85% of 2-arachidonoylglycerol (2-AG), the primary cannabinoid 1 (CB1) receptor ligand. Understanding MAGL's in vivo role is vital, as MAGL inhibitors have demonstrated potential across various therapeutic targets. This study aims to conduct the first-in-human evaluation of the novel PET radiotracer [^{18}F]MAGL-2102 for MAGL.

Purpose: This study aims to (1) evaluate [^{18}F]MAGL-2102's in vivo safety, binding, biodistribution, and pharmacokinetics in healthy controls, (2) quantify radiation dose distribution across organs, and (3) assess tracer reliability and consistency over time.

Methods: Ten healthy volunteers (aged 19–65) will undergo a 120-minute brain PET/CT scan with 185 MBq (±10%) [^{18}F]MAGL-2102, followed by a repeat scan one month later. An additional whole-body dynamic 3D scan will be conducted with 85 MBq (±10%) [^{18}F]MAGL-2102 over 120 minutes.

Preclinical Results: One female participant successfully completed the first-in-human [^{18}F]MAGL-2102 brain scan, confirming blood-brain barrier penetration with a stable SUV of 0.7 throughout. Tracer distribution was highest in the cortex and lowest in white matter. Logan graphical analysis demonstrated linearity, indicating a reversible radioligand. Minimal metabolism was observed, with ~90% of the parent tracer remaining intact by the end of the scan.

Conclusion: Based on this single scan, further validation is needed to confirm [^{18}F]MAGL-2102's suitability for imaging MAGL. However, these preliminary findings align with preclinical results in non-human primates. Evaluating [^{18}F]MAGL-2102 in humans is a crucial step toward accurate MAGL quantification, advancing PET research, and accelerating targeted therapies for neuropsychiatric disorders.

D: Neuroscience & Brain Health

D.1: Minocycline as adjunctive treatment for treatment-resistant depression: A double blind, placebo-controlled, randomized trial (MINDEP2)

Student: Mary (Lily) Kittur, Supervisor: Ishrat Husain

Background: Accumulating evidence implicates immune dysfunction in the pathophysiology of treatment-resistant major depression (TRD), proposing immunomodulatory augmentation as a novel treatment strategy. The second-generation tetracycline minocycline is well-tolerated and demonstrates anti-inflammatory effects on several immune pathways associated with TRD. Previous trials evaluating minocycline augmentation in TRD have been underpowered and limited by methodological heterogeneity, highlighting the need for larger scale replication.

Purpose: The primary objective of this 12-week, placebo-controlled trial is to establish the safety and efficacy of minocycline added to standard antidepressants in adults with TRD. The exploratory objective is to assess whether minocycline response is mediated by changes in circulating inflammatory markers.

Hypotheses: 1) Patients receiving adjunctive minocycline will show a greater reduction in depressive symptoms from baseline to week 12 than those receiving placebo. 2) There will be no significant difference in the frequency of reported adverse events between groups. 3) TRD patients with biochemical evidence of inflammation at baseline will show a greater response to minocycline. 4) Change in depressive symptoms from baseline to week 12 will be mediated by change in peripheral immune markers.

Methods: This was a double-blind, parallel arm trial in which subjects were randomized 1:1 to receive oral minocycline or placebo added to standard antidepressants. We enrolled 76 adults (aged >18) with a DSM-5 diagnosis of MDD and previous failure to respond to conventional treatments per the Antidepressant Treatment History Form (ATHF). Primary clinical outcome was change in depressive symptoms from baseline to week 12 as measured by the 17-item Hamilton Depression Rating Scale (HRSD-17). Blood samples collected at baseline, week 6, and week 12 will be assayed to determine levels of pro-inflammatory cytokines and C-reactive protein (CRP).

Expected Results: Primary data collection has been completed with a retention rate of 70% (53/76) at week 12 endpoint. Data is currently blinded with statistical analyses projected over the next few months. Following the intent-to-treat (ITT) approach, I will use a mixed-effects linear model to evaluate differences in HDRS-17 score change from baseline to week 12 between minocycline and placebo groups. Differences in adverse event frequency will be assessed through generalized linear regression. I will explore predictors of minocycline response by interacting baseline levels of putative inflammatory biomarkers with the primary treatment model. Mediation effects will be tested using a Latent Growth Model in which change in HDRS-17 is specified as going through change in inflammatory biomarkers.

Conclusions: If findings confirm the tolerability and antidepressant properties of minocycline, it warrants consideration as a genuinely novel adjunct treatment for TRD. Biomarker analysis hopes to identify measurable predictors of minocycline response, and in doing so inform individualized treatment strategies for a subset of patients demonstrating immune reactivity.

Clinicaltrials.gov identifier: NCT03947827

D.2: Examining the neurophysiological effects of psilocybin: A narrative review

Student: Renee Lawson, Supervisor: Daphne Voineskos

Purpose: Psilocybin, a $5HT_{2A}$ agonist extracted from the psilocybe mushroom, has resurfaced in the field of psychiatric treatment, with promising potential for multiple disorders. However, psilocybin's specific mechanisms of action on human neurophysiology are not fully understood. This narrative review aims to examine the existing literature regarding psilocybin's neurophysiological effects in humans and address any gaps that should be investigated in the future.

Methods: PubMed and EMBASE were searched on June 15th, 2024, using the following terms: "((psilocybin AND neurophysiology) OR (psilocybin AND cortical inhibition) OR (psilocybin AND cortical excitation) OR (psilocybin AND plasticity) OR (psilocybin AND LTP) OR (psilocybin AND LTD) OR (psilocybin AND EEG) OR (psilocybin AND MEG) OR (psilocybin AND fMRI) or (psilocybin AND PET) OR (psilocybin AND MRS)". Studies were included if the following criteria were met: (1) primary research article published after 1980, (2) in English, (3) involving human participants.

Results: 823 studies were imported to Covidence for screening and 357 were removed due to duplication. 466 studies went through title and abstract screening; 342 were deemed irrelevant. 124 studies went through full-text review, with 58 included in the final sample. EEG measures of perceptual and attention-related processing such as component amplitudes extracted from VEPs and ERPs consistently decreased in healthy individuals post-psilocybin administration**.** Furthermore, a desynchronizing effect observed in network-specific activity within healthy individuals, with increased entropy in the DMN, ECN and Dorsal Attention networks observed via fMRI studies, as well as an increase in spatiotemporal dynamics and MEG variability, reinforced by decreases in functional connectivity. In contrast, when examining global brain activity with phase-lock analysis, there appeared to be an increase in coherence. Many fMRI studies consistently reported decreased regional-specific cerebral blood flow and blood- oxygen-level dependent (BOLD) signal in healthy individuals post-psilocybin, most commonly within the amygdala. Lastly, a relatively consistent pattern of right hemisphere increases of glucose metabolism were reported through PET and MRS studies after psilocybin**.**

Significance: Investigations regarding psilocybin's therapeutic benefits continue to be underway at many major institutions, making it increasingly important that the neurophysiological underpinnings of this compound continue to be studied and understood. The knowledge gaps identified in this review may help direct future research efforts within this field.

D.3: Spectral signatures of psilocybin, lysergic acid diethylamide (LSD) and ketamine in healthy volunteers and persons with major depressive disorder and treatment-resistant depression: A systematic review

Student: Gia Han Le, Supervisor: Roger McIntyre

Background: Electrophysiologic measures provide an opportunity to inform mechanistic models and possibly biomarker prediction of response. Psilocybin, lysergic acid diethylamide (LSD), and ketamine represent new investigational and established treatments in mood disorders respectively. There is a need to better characterize the mechanism of action of these agents.

Methods: We conducted a systematic review investigating the spectral signatures of psilocybin, LSD, and ketamine in persons with major depressive disorder (MDD), treatment-resistant depression (TRD), and healthy controls.

Results: Ketamine and serotonergic psychedelics (SDs) are associated with increased spectral power of the theta bands in persons with depression. Ketamine and SPs are also associated with decreased spectral power in the alpha, beta and delta bands in both healthy controls and persons with depression. Spectral power of theta bands was increased in persons with MDD when administered with SPs. Ketamine is associated with increased gamma band power in both healthy controls and persons with MDD.

Conclusions: Extant literature evaluating EEG and MEG spectral signatures indicate that psilocybin, LSD, and ketamine have reproducible effects in keeping with disease models of network connectivity. Future research vistas should specifically evaluate whether observed spectral signatures can guide further discovery of therapeutics within the psychedelic and dissociative classes of agents, and its prediction capability in persons treated for depression.

D.4: "Autism diagnosis as a guide": The lived experiences of autistic adolescents receiving an autism diagnosis in Taiwan

Student: Chun-Hao Liu, Supervisor: Meng-Chuan Lai

Background: Autistic individuals frequently face social difficulties and stigmatization in neurotypical-dominant societies. However, little is known about how autistic adolescents experience receiving an autism diagnosis and how the diagnosis influences their daily lives in a non-Western cultural context.

Purpose: This study aims to explore the experiences of Taiwanese autistic adolescents receiving autism diagnoses and how these diagnoses affect their lives and social navigation.

Methods: Eight autistic adolescents aged 14-18 (3 assigned-male-at-birth, 5 assigned-female-at-birth) participated in in-depth individual interviews. They were diagnosed with autism between the ages of 8 and 18, with diagnoses received 0–7 years prior to the interviews. All interviews (average duration: 43 minutes) were audio-recorded, transcribed verbatim, and analyzed using thematic analysis.

Results: The autistic adolescents in Taiwan expressed obvious agency in living with autism diagnosis. They used their autism diagnoses: (a) to explain past lived experiences with both positive and negative stereotypes; (b) as a guide to autism knowledge and providing a framework for modifying own behaviors; (c) to seek a sense of belonging from autistic peers, and facilitating understanding from non-autistic people; and (d) to negotiate with the regulations of the Taiwanese educational system to meet their needs.

Conclusion: Our findings highlight the subjectivity and agency of autistic adolescents in receiving an autism diagnosis within a Taiwanese cultural context. They used the diagnosis as a tool to better understand themselves, reframe their identities, gain the sense of belonging, and interact with their environments, including family, peers, and the education system.

D.5: The effects of STN DBS on hippocampal volumes in Parkinson's patients

Student: Suraiya Mangra, Supervisor: Andres M. Lozano

Background: Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is an approved surgical intervention for advanced Parkinson's Disease (PD) due to its unparalleled ability to reduce both its motor symptoms and the dosage of required medications, such as levodopa. Despite these symptomatic improvements, little is known about how STN DBS impacts brain morphology. Existing neuroimaging studies have been limited by small sample sizes, lack of control groups of PD patients without DBS, and scarcity of magnetic resonance imaging (MRI) data. Cognitive studies have found mixed results, particularly for domains of memory and learning. This makes the hippocampus a region of interest when examining DBS outcomes. Neuroimaging studies on the hippocampus have been limited to unilaterally implanted patients and show equally mixed results, with one study deriving an annual atrophy rate of 13.9% +/- 15.8%, while another found a modest decline of 2-3% annually.

Purpose: The primary objective of this study was to determine if STN DBS accelerates hippocampal atrophy by comparing DBS longitudinal volume changes to PD patients without DBS using T1-weighted MRI. This study's secondary objective was to determine if cognitive findings aligned with volume outcomes using memory and global cognitive assessments.

Hypotheses: It was expected that STN DBS and PD control cohorts will experience hippocampal atrophy, but patients that had greater cognitive decline at baseline will experience greater longitudinal volume loss. It was believed that cognition would align with volume findings.

Study Design: 76 STN DBS (mean age = 60, Bilateral = 65, LS = 7, RS = 4) , 121 PD patients from the Ontario Neurodegenerative Disease Research Initiative (ONDRI, mean age = 68)), and 244 PD patients from the Parkinson's Progressive Markers Initiative (PPMI, mean age = 62) were selected for this study. Hippocampal volumes were obtained using SynthSeg+, an automatic deep learning segmentation tool that was validated using intraclass correlation coefficients (ICC's) of 52 manual segmentations (LS ICC = 0.84, RS ICC = 0.85). Longitudinal volume and cognitive score changes were assessed using mixed effect linear models due to varying time points between follow-ups and varying number of follow-ups between each patient.

Results: Mixed effect linear models found that the number of days since baseline predicted hippocampal volumes in most groups, but low estimates (DBS RS estimate = -0.199, DBS RS p <0.001, ONDRI LS estimate = -0.138, RS estimate = -0.145, ONDRI LS and RS p <0.001, PPMI LS and RS estimate = -0.1, PPMI LS and RS p < 0.001). Estimates of daily volume change converted to annual percentage volume changes, which yielded a 1-2% annual atrophy rate in all groups. Cognitive results found decline in global cognition (estimate = -0.003, p <0.001) and verbal learning (estimate = -0.001, p = 0.005) performance in DBS patients, while decline in immediate and delayed visuospatial memory (immediate estimate = -0.002, p = 0.003, delayed estimate <0.001, p = 0.01) and naming (estimate <0.001, p = 0.03) was found in the ONDRI patients. However, small estimates suggest minimal change. PPMI patients remained stable and no strong correlations were found between volumes and cognitive scores.

Conclusion: STN DBS and control PD groups found similar hippocampal annual percentage atrophy rates of 1-2%, which is comparable to existing recorded rates of decline of healthy aging people. Cognitive findings in both groups were minimal over time based on low estimates from mixed models. However, cognitive results do not correlate to hippocampal volumes.

D.6: Genetic links between sleep fragmentation and Alzheimer's disease

Student: Aishwaria Maxwell, Supervisor: Andrew Lim

Background: Individuals with dementia often experience sleep disturbances. Observational studies have revealed associations between sleep disturbance and cognitive impairment in elders. In vivo studies have demonstrated ways in which sleep deprivation affects the pathophysiological pathways involved in Alzheimer's disease pathogenesis. Some studies in elderly and middle-aged individuals have shown that sleep deprivation precedes cognitive impairment and Alzheimer's disease onset. However, Alzheimer's disease pathology begins decades before symptom onset, thus the causal effect of sleep deprivation on Alzheimer's Disease is unclear. To address this gap, genetic techniques such as Mendelian Randomization can be used to suggest casualty.

Purpose & Hypothesis: This study will disambiguate the direction of causal links between sleep disruption, dementia-related brain changes, and cognitive impairment. Sleep deprivation will be causally associated with Alzheimer's disease. Sleep deprivation will be measured using the sleep fragmentation metric, k_{RA}.

Methods: A genome-wide association analysis (GWAS) in adults of European ancestry from UK Biobank was conducted to identify genetic instrumental variables of sleep fragmentation. Associations of these variants with other sleep measures was also be determined. A two-sample Mendelian Randomization (MR) using an inverse variance weighted approach was conducted along with sensitivity analyses using MR-Egger and weighted median estimation.

Results: The GWAS identified 3 risk loci for sleep fragmentation. Tissue expression analysis revealed expression of SNPs in the heart, blood vessels, and several regions of the central nervous system. MR revealed no significant causal associations in either direction.

Conclusions: Our results are inconclusive and suggest that additional analysis be completed to further ascertain the relationship between sleep deprivation and Alzheimer's disease.

D.7: The insula as a biomarker for substance use disorders: An ENIGMA Consortium study

Student: Nafia Mirza, Supervisor: Bernard Le Foll, Colin Hawco

Background: Substance use disorders (SUD) involve compulsive substance seeking and consumption despite adverse consequences. Neuroimaging studies have identified cortical volume reductions in key brain regions, including the insula, frontal lobes, and anterior cingulate cortex, across various substances. The insula has emerged as a promising target for brain stimulation therapies, such as repetitive transcranial magnetic stimulation (rTMS). However, further research is needed to understand its structural and functional interactions with other brain regions as potential biomarkers of SUD. The Enhancing NeuroImaging Genetics through Meta-Analysis (ENIGMA) Consortium, an international collaborative network, integrates neuroimaging, genetics, and cognitive data from multiple institutions. The Addictions Working Group consists of numerous neuroimaging sites and thousands of participants, providing a unique opportunity to examine shared and distinct neurobiological mechanisms underlying addiction across different substances.

Objectives: For this project we have 3 aims: 1) to understand how insula dysfunction affects other brain regions in relation to addiction; 2) to understand how insula dysfunction relates to other functional regions in the brain; and 3) to investigate any differences in insula function across different types of addictive substances.

Hypotheses: 1) decreased cortical thickness of the insula is correlated with the magnitude of SUD; 2) insular deficits will be identified by decreased functional connectivity with the salience network and basal ganglia; and 3) addictions to illicit substances will result in a greater magnitude of deficits (i.e decreased thickness and functional connectivity) in the insula and neighboring regions compared to controlled substances, such as nicotine and alcohol.

Methods: For aim 1, cortical thickness will be extracted using Freesurfer, and structural covariance analysis will assess the impact of insular atrophy on other brain regions. To address aim 2, Resting-state fMRI data will be analyzed to examine functional connectivity differences between SUD patients and healthy controls, focusing on interactions between the insula, salience network and basal ganglia. Finally, to address aim 3, cortical thickness and functional connectivity measures will be compared across substance categories (psychostimulants, opiates, and tobacco) to identify substance-specific differences. Cross-validation techniques will be employed to ensure the robustness of findings.

Significance: With access to thousands of participant data, we will have the statistical power to generate robust analyses and findings that will bring us closer to understanding the role of the insula as a biomarker for treatment and therapies of SUDs. Understanding the interactions between the insula and other brain areas may provide new opportunities for targeted and optimized brain stimulation. Identifying biomarkers could also enhance SUD treatment by building predictive models and estimating risk at different stages, or helping guide ideal treatment selection in a more individualized way.

D.8: Neural adaptations to new cochlear implants: A longitudinal electroencephalogram study

Student: Shimin Mo, Supervisor: Andrew Dimitrijevic, Claude Alain

Background: Cochlear implants (CIs) can help improve auditory function, but post-implantation outcomes vary widely and often do not correlate well with each other. Standard clinical tests (e.g., AzBio) assess speech perception in controlled environments but overlook cognitive demands, such as selective attention, that are critical for real-world speech-in-noise listening. Consequently, these tests do not effectively predict Patient-Reported Outcome Measures (PROMs), which reflect the daily listening challenges faced by CI users.

Purpose and Hypotheses: To address these gaps, this study aims to (1) examine post-CI neural adaptation trajectory using ecologically valid tests and (2) evaluate their predictive value for PROMs. It is hypothesized that new CI users' psychophysical, behavioural speech perception and PROMs improve over one year, and ecologically valid test performance better predicts subjective PROMs than standard clinical tests.

Methods: Eighteen newly implanted CI users participated in four sessions (0-, 3-, 6-, and 12-months post-activation), completing behavioral digits-in-noise (DiN) and EEG audiobook listening tasks. In both tasks, participants attended to a target speaker while ignoring distractors varying in speaker identity and location (DiN) or identity only (EEG). Lower speech-distractor threshold and greater Temporal Response Function (TRF) weights indicate better objective speech perception outcomes.

Results: Speech-distractor threshold significantly decreased over time. TRF analysis of current data (n = 7) revealed an approaching-significance session effect, suggesting neural adaptations in cognitively demanding speech tracking over time. Linear mixed-effects modeling showed significant interactions between session and both TRF and DiN performance in predicting PROMs within the speech domain.

Conclusions: Preliminary findings suggest that neural adaptations to continuous speech tracking improve post-CI, with distractor identity influencing the magnitude of improvement. These ecologically valid measures could guide the development of personalized, long-term interventions to enhance CI outcomes.

E: Neuroscience & Brain Health

E.1: Sex-specific neuroprotective effects of conjugated GLP-1 and estradiol (GE2) in Alzheimer's disease: Implications for metabolic and neuronal modulation

Student: Ahmad Mohammad, Supervisor: Liisa Galea

Background: Alzheimer's disease (AD) is the leading cause of dementia worldwide, marked by progressive memory loss and neuronal death. Notably, two-thirds of AD patients are female, and many carry the APOE4 allele, implicating sex and genotype as key risk factors. Inflammation, metabolic dysregulation, and impaired hippocampal neurogenesis are central to AD pathology. Although estradiol and glucagon-like peptide-1 (GLP-1) individually confer neuroprotection, their conjugated form (GE2) may offer enhanced benefits.

Purpose any Hypothesis: This study investigates whether GE2 improves cognitive function and modulates hippocampal neuroplasticity and inflammation in male and female huAPOE4 x 5XFAD and huAPOE3 x 5XFAD mice. We hypothesize that GE2 will enhance cognition and neuroplasticity while reducing neuroinflammation in a sex-dependent manner, with pronounced benefits in metabolically challenged animals.

Methods: Mice will be metabolically challenged with a Western diet (high fat, high sucrose) for six weeks to induce obesity, then treated with GE2 or placebo for four weeks. Cognitive assessments, including contextual and cued fear conditioning, along with glucose tolerance tests, will be performed. Brain tissue will be analyzed via MesoScale Discovery assays to quantify cytokines and AD markers, and immunohistochemical analyses will evaluate neurogenesis and microglial activation. Additional hormone profiling by mass spectrometry will further elucidate GE2's systemic effects.

Results: We anticipate that GE2 will enhance cognitive function, promote neuroplasticity, and reduce neuroinflammation, particularly in metabolically challenged animals, with sex-dependent effects. Conclusions: This study addresses a critical gap in understanding the interplay of sex, metabolism, and neuroinflammation in AD, potentially establishing GE2 as a novel, sex-specific therapeutic strategy for mitigating AD progression. Elucidating how GE2 modulates neuroinflammatory and neurogenic pathways may inform personalized treatment approaches, ultimately improving outcomes for AD patients, particularly women in Canada.

E.2: Chronic stress-induced alterations to the activation of new neurons during negative cognitive bias

Student: Amanda Namchuk, Supervisors: Liisa Galea

Background: Major depressive disorder (MDD) is a debilitating illness characterized by depressed mood, a lack of motivation, and cognitive deficits. 2x more females than males have been diagnosed with MDD and there are sex differences in manifestation of the disease. MDD is associated with decreased neurogenesis and aberrant neural activity in the dorsal and ventral hippocampus (dHPC & vHPC). Negative cognitive bias (NCB), or the interpretation of ambiguous stimuli as negative, is a treatment-resistant cognitive symptom of MDD that we can model in rodents using the cognitive bias task developed in the Galea Lab. Chronic unpredictable stress (CUS) induces depressive-like endophenotypes in rodents of both sexes. Previous work in the lab has demonstrated that CUS increases NCB in both male and female rats, with no sex differences in behaviour. However, there are extensive sex differences in the underlying neurobiology. The role of neurogenesis and activation of new neurons in NCB remains unexplored.

Purpose and Hypothesis: The aim of this study is to investigate sex-specific, CUS-induced alterations to neurogenesis and the activation of new neurons during negative cognitive bias. Based on previous findings, we expect to see an increase in NCB in CUS-exposed males and females compared to non-CUS exposed controls. Further, we hypothesize that CUS-exposed rats of both sexes will show a decrease in neurogenesis, but there will be sex differences in the way new neurons are used (location of activated new neurons, quantity of activated new neurons, age of activated new neurons, etc.) during the cognitive bias task.

Methods: We exposed young adult male and female Sprague-Dawley rats to 21d of CUS or no-CUS (NS) then administered the NCB task developed in the lab. To model cognitive bias, we trained rats to discriminate between a shocked and non-shocked context over 16d. Throughout training, rats display their natural fear response, freezing, in anticipation of the shock they will receive in the shocked context. They also learn that the non-shocked context is safe, and then freeze very little in that context. On day 18, we tested them in an ambiguous context with a mix of cues from the shocked and non-shocked contexts where high freezing indicates NCB and low freezing indicates a more neutral or positive bias. Animals were sacrificed 90 mins after testing. Using immunohistochemistry, we stained brain sections containing dHPC and vHPC for markers of new neurons that are 4 weeks old (BrdU), 2 weeks old (doublecortin, DCX), and active during testing (cFos). BrdU, a thymidine analogue that is incorporated into the DNA of proliferating cells, can be used to birthdate cells born on the day it is administered (4 weeks before testing). DCX is an endogenous microtubule-associated protein that is expressed in immature neurons up to 2 weeks old. cFos is an immediate early gene expressed after neural activity. Together, these markers allow us to quantify the total number of 4-week-old cells (BrdU+), the number of 4-week-old cells that were active during testing (BrdU+/cFos+), the total number of 2-week-old cells (DCX+), and the number of 2-week-old cells that were active during testing (DCX+/cFos+).

Results: Replicating previous results, we found that CUS increased NCB in both sexes. CUS also reduced the activation of 2-week-old neurons (DCX+/cFos+) in the vHPC, but not dHPC, of CUS-exposed males and females. Further quantification is ongoing, but preliminary findings suggest that stress disrupts the integration of new neurons into the circuitry used to interpret the ambiguous context.

E.3: Vitamin D mediated mechanisms in autoimmune disease

Student: Guy Nevo, Supervisor: Matthew R. Lincoln

Background: Autoimmune and inflammatory disorders are complex traits caused by numerous genetic and environmental factors. Genetic studies have identified many risk loci for these diseases. Genetic risk variants are characteristically non-coding and enriched in open chromatin regions that are active in immune cells; they are likely to influence gene expression in immune cells, but we do not know the precise downstream targets for most risk loci. Low Vitamin D is strongly associated with multiple sclerosis (MS): high latitude and low ultraviolet exposure predict higher MS risk. Month of birth and migration studies provide additional evidence for low vitamin D contributing to MS pathogenesis. Mendelian randomization studies confirm that low serum vitamin D itself—not an unmeasured confounder—is a causal risk factor for MS. We do not know precisely how low vitamin D causes MS, but vitamin D is a potent transcriptional regulator, particularly in immune cells.

Purpose and Hypothesis: We hypothesize that the pathways regulated by vitamin D in immune cells are relevant to autoimmune pathogenesis and that these may interact with genetic risk. To identify autoimmune disease mechanisms, we propose to characterize the transcriptional effects of vitamin D over time in human immune cells at single-cell resolution.

Methods: We collected whole blood samples from 10 healthy subjects. Using a density gradient, we isolated peripheral blood mononuclear cells (PBMCs). We then cultured PBMCs with and without the active form of vitamin D ($1,25(OH)_2$-D_3). We assessed gene expression at 8-, 24-, 48- and 72 hours using the 10x Flex assay. After alignment to the human genome, quality control, and identification of discrete cell type populations in our data, we obtained data on a total of 563,520 human PBMCs.

Expected Results: We will identify genes that are differentially expressed in functionally relevant immune cell subsets (e.g. CD_4 T cells, monocytes, B cells) between the control and vitamin D conditions. We will control for inter-subject variability. We will explore mixed models to identify independent effects of sex, age and baseline serum vitamin D level ($25(OH)D_3$). Through gene set and pathway analysis, we will identify up- and down-regulated pathways at different time points across treatment conditions, which will enable us to identify potential immune mechanisms that are affected by vitamin D. We will overlay GWAS and eQTL data from 19 different autoimmune diseases to verify the relevance of the identified genes, pathways, and mechanisms across different autoimmune diseases and possibly identify shared mechanisms between them.

E.5: Exploring the role of capicua (CIC) in modulating sensitivity to MEK inhibitors in glioblastoma

Student: Phooja Persaud, Supervisor: Gelareh Zadeh

Background: Glioblastoma multiforme (GBM) is the most common and lethal primary brain tumor, characterized by resistance to conventional therapies. Despite its heterogeneity, a central feature of GBM is dysregulated kinase signaling. Specifically, the hyperactivation of receptor tyrosine kinases (RTKs) and their downstream MEK/ERK pathway contribute to GBM's aggressive behavior. Capicua (CIC) is a high-mobility group (HMG)-box transcriptional repressor that directly binds to DNA, suppressing the transcription of genes typically activated by RTK signaling, such as oncogenic transcription factors ETV1/4/5. We discovered that CIC forms a repressor complex with Ying Yang 1 (YY1), inhibiting the expression of tumorigenic genes. However, hyperactivation of MEK/ERK signaling leads to the degradation of this complex, promoting tumorigenesis. Interestingly, sustained MEK inhibition failed to restore CIC protein levels and instead resulted in the reactivation of p90RSK, a downstream effector of ERK and a known regulator of CIC.

Purpose & Hypothesis: CIC, though critical in cancer biology, remains underexplored, particularly in the context of resistance to RTK/MEK/ERK inhibitors. Understanding how CIC's repressive function is regulated will provide crucial insights into potential therapeutic strategies for overcoming resistance to RTK/MEK/ERK inhibition in GBM. We hypothesize that inhibition of p90RSK stabilizes the CIC/YY1 co-repressor complex, re-sensitizing GBM cells to MEK/ERK inhibitors.

Methods: Patient-derived glioma stem cells (GSCs) were treated with increasing doses of two p90RSK inhibitors, BI-D1870 or LJI308, both in the presence and absence of selumetinib (a MEK inhibitor). Various functional assays were performed to assess the effect of p90RSK inhibition on the CIC/YY1 complex and GSC sensitivity to MEK inhibition.

Results: Treatment with BI-D1870 and LJI308 significantly reduced GSC viability and mRNA expression of ETV1/4/5, suggesting that p90RSK inhibition may restore CIC/YY1 repressive activity. Importantly, p90RSK inhibition also sensitized GSCs to MEK inhibition.

Conclusion: These findings highlight the critical role of p90RSK inhibition in stabilizing the CIC/YY1 co-repressor complex and enhancing GBM cell sensitivity to RTK/MEK/ERK pathway inhibitors. This strategy presents a promising approach to overcoming therapeutic resistance in GBM.

Results to Date: My preliminary results show a decreased latency to first spike and first seizure and increased seizure duration in $Nf1^{flox/vGlut}$ mice versus $Nf1^{flox/PV}$ mice, suggesting that excitatory cells drive the altered seizure susceptibility we previously reported in $Nf1^{+/-}$ mice.

E.6: Evaluation of N-back working memory task using electroencephalography and magnetoencephalography in psychiatric disorders: A systematic review

Student: Viet-Linh Luke Pham-Kim-Nghiem-Phu, Supervisor: Pushpal Desarkar

Background: Working memory (WM) deficits are common across psychiatric disorders, significantly affecting functional outcomes. The N-back is a widely used task to assess WM. Concurrently administering electroencephalography (EEG) and magnetoencephalography (MEG) with N-back can provide insights into potential mechanisms and identify biomarkers underlying WM deficits.

Purpose: This review investigated variations and relationships across N-back performance and EEG/MEG metrics in psychiatric disorders.

Methods: PubMed, PsycINFO, and EMBASE were searched until December 31st, 2023 for research articles published in English. All studies used EEG or MEG during the N-back in DSM-IV and DSM-5 psychiatric disorders. Review articles, animal studies, and abstracts were excluded. Information was extracted on demographics, clinical characteristics, N-back performance and EEG/MEG metrics and related results, recording and processing parameters, and intervention effects. This protocol was registered with PROSPERO [CRD42024506489].

Results: 34 studies met the criteria (EEG: 27, MEG: 7). While relationships between N-back and EEG/MEG metrics varied, almost all EEG studies on theta-gamma coupling found positive associations with N-back accuracy. EEG studies analyzing event-related potentials found reduced amplitudes in schizophrenia, minor and major neurocognitive disorders, attention deficit hyperactivity disorder, and specific phobias. MEG studies in autism consistently found reduced theta connectivity compared to controls. Significant variations in EEG/MEG metrics were observed in most studies assessing changes across N-back WM load and in studies assessing intervention effects.

Conclusion: This review underscores the utility of N-back EEG/MEG metrics in examining biological mechanisms underlying WM deficits. In particular, theta connectivity and theta-gamma coupling could be further explored as potential neurophysiological markers for WM deficits across psychiatric disorders.

E.7: Exploring polygenic risk for insomnia in relation to sleep disturbance and psychiatric correlates in youth

Student: Alexandra Puchiele, Supervisor: Benjamin Goldstein

Background: Sleep disturbance is common in youth with depression and is correlated with mood symptom burden. Insomnia polygenic risk (PRS), computed from adult genome-wide association study (GWAS) data, is associated with sleep disturbance among youth in the general population. However, no studies have validated insomnia-PRS in a clinical sample of youth with depression.

Purpose and Hypothesis: This study aims to validate the generalizability of insomnia-PRS, derived from adult GWAS, in a well-characterized sample of youth with and without depression. *Hypothesis 1*: Insomnia-PRS will be associated with sleep disturbance in the overall sample. *Hypothesis 2:* Insomnia-PRS will be associated with more severe psychiatric characteristics in youth with depression.

Methods: Participants included 400 youth aged 13-21 (273 with lifetime depression [161 bipolar disorder, 112 major depressive disorder] and 127 healthy controls). Insomnia-PRS was computed from adult GWAS. Sleep disturbance was derived from most severe lifetime insomnia and hypersomnia items from the Kiddie Schedule for Affective Disorders and Schizophrenia Depression Rating Scale. General linear models examined main effects of insomnia-PRS on sleep disturbance and psychiatric correlates (mood, anxiety, suicidality, functioning), controlling for age, sex, body mass index, and two genetic principal components.

Results: Insomnia-PRS was higher in youth with depression vs. healthy controls (p=0.04, d=0.22), and was significantly associated with insomnia severity (η^2p=0.02, p=0.02) in the overall sample. Among youth with depression, insomnia-PRS was significantly associated with insomnia severity in females (η^2p=0.04, p=0.01), but not males (η^2p=0.002, p=0.76). The association between insomnia-PRS and lifetime suicidal ideation trended towards significance (η^2p=0.02, p=0.07). There were no significant findings for hypersomnia.

Conclusions: This study extended prior findings linking adult-derived insomnia-PRS with sleep disturbance in youth with depression, with evidence of sex differences. Insomnia-PRS may relate to suicidal ideation, further underscoring the importance of the sleep-depression interface in youth.

E.8: Dissecting the phenotypic spectrum and complexity of movement disorders in 22q11.2 deletion syndrome

Student: Nikolai Gil Reyes, Supervisor: Anthony E. Lang

Background and Purpose: Movement disorders are increasingly recognized as late-occurring neurologic manifestations of 22q11.2 deletion syndrome (22q11.2DS). We aimed to dissect the spectrum of relevant movement disorders in 22q11.2DS, including clinical and electrophysiologic presentations and effective therapies.

Methods: Retrospective review of medical records, medication histories, and videotaped examinations was conducted in 31 adults (55% female) diagnosed with 22q11.2DS and a movement disorder who were seen at a major center of excellence from June 1996 to September 2023. Between-group comparisons were performed to explore the influence of medications on movement disorder presentations.

Results: The median age at movement disorder onset was 35.5 (IQR: 22.0) years. Non-parkinsonian tremor was the most common phenotype (21/31, 68%), followed by parkinsonism (13/31, 42%), dystonia (11/31, 36%), myoclonus (9/31, 29%), dyskinesia (6/31, 19%), stereotypies, and functional movement disorders (4/31, 13% each). The majority of patients (24/31, 77%) presented with two or more movement disorder phenotypes (median 3, range: 2-7). Similar trends in prevalence emerged after accounting for antipsychotic exposure and potential drug-related movement disorders. Electrophysiological assessments identified both previously described and novel motor phenotypes. Treatment data for at least one movement disorder (available for 20/31, 65%) indicated a positive response to standard phenotype-based interventions.

Conclusions: We demonstrate that movement disorders in adults with 22q11.2DS exhibit greater clinical complexity than previously reported, which could reflect innate vulnerability and pathologic mechanisms beyond medication side effects. In those with a confirmed 22q11.2 microdeletion, periodic neurologic evaluations, supported by electrophysiologic investigations, enable accurate diagnosis and implementation of personalized management strategies.

F: Neuroscience & Brain Health

F.1: Investigating the role of *apolipoprotein E4* on cognitive impairment in Parkinson's disease: Insights from structural MRI measures in the PPMI cohort

Student: Angenelle Rosal, Supervisor: Antonio Strafella

Background: Cognitive impairment is a prevalent non-motor symptom of Parkinson's Disease (PD), yet the factors driving its onset and progression remain poorly understood. *Apolipoprotein E4 (APOE4),* a genetic risk factor of Alzheimer's Disease, has been associated with PD-related cognitive impairment. However, the role of *APOE4* in this non-motor symptom of PD is still unclear due to contradictory findings in the literature. Notably, both cognitively impaired PD patients and *APOE4* carriers independently exhibit gray matter abnormalities, specifically reductions in gray matter volume (GMV) and cortical thickness (CT). However, no study has explored the relationship between *APOE4* status, GMV and CT measures, and cognitive function, all together in a PD cohort.

Purpose: The purpose of this study is to clarify the role of *APOE4* on PD-related cognitive impairment by investigating its effects on GMV and CT.

Hypothesis: We hypothesize that PD *APOE4* carriers will exhibit significant decreases in GMV and CT in regions previously associated with *APOE4* and cognition when compared to PD *APOE4* non-carriers. Furthermore, decreases in GMV and CT in these regions in PD *APOE4* carriers will be correlated with worsened cognitive performance.

Methods: Baseline T1-weighted Magnetic Resonance Imaging (MRI) scans from 52 PD *APOE4* carriers (58.9 ± 9.2 years; 16 females, 36 males) and 123 PD *APOE4* non-carriers (63.1 ± 9.1 years; 75 males, 48 females) were acquired from the Parkinson's Progression Markers Initiative (PPMI) database. Scans were processed in FreeSurfer 7.1 to extract GMV and CT measures. Group differences in GMV and CT for regions defined by the Desikan-Killiany Atlas were assessed using independent t-tests and ANCOVAs controlling for age, sex, and disease duration. Pearson correlations examined relationships between significantly different regions and 9 cognitive tests.

Results: Preliminary analyses revealed significant GMV differences between PD *APOE4* carriers and non-carriers in the right lateral occipital, left inferior parietal, and left superior parietal cortices. GMVs of the first two regions correlated with Hopkins Verbal Learning Retention Test scores, while GMV of the left superior parietal cortex correlated with Montreal Cognitive Assessment scores. No significant differences were observed in CT measures.

Conclusions: These preliminary findings suggest that *APOE4* may impact the GMV of regions linked to cognitive performance in PD, but not CT, highlighting its potential as an early biomarker or therapeutic target for PD-related cognitive impairment. Further analysis will be conducted to verify these relationships.

F.2: Does peri-operative dexmedetomidine have an effect on depressive symptoms after cardiac surgery? A CODEX sub-study

Student: Hannah Rose Rosales, Supervisor: Stephen Choi

Background: The incidence of postoperative depressive symptoms is higher in those undergoing larger, more invasive surgery, than in those undergoing less invasive procedures or no surgery. For example, incident depression higher 5 years after Coronary Artery Bypass Grafting (OR 2.33). This is higher compared to other surgical types, possibly secondary to the fact that CABG is amongst the most invasive procedures. The sedative dexmedetomidine, a selective α2-adrenergic agonist, shows potential in reducing postoperative depressive symptoms. Examining dexmedetomidine-sedation effects on postoperative mood warrants further investigation, particularly after cardiac surgery as this patient population suffers from a higher incidence of postoperative depressive symptoms than other surgical patients.

Purpose and Hypothesis: Our project aims to determine the incidence of new or worsened depression symptoms in cardiac surgery patients following dexmedetomidine-based versus standard sedation protocols in the cardiovascular intensive care unit (CVICU). There is early data in the psychiatry population that dexmedetomidine may help mood. We hypothesize that those who receive dexmedetomidine will have less depressive symptoms 3 months after surgery.

Methods: Data is collected as part of the ongoing CODEX Trial. CODEX is a prospective randomized-control multicentre trial investigating the efficacy of dexmedetomidine in reducing persisting postoperative neurocognitive disorder compared to standard sedation protocol during initial CVICU recovery. Patients (age≥60) undergoing open-heart surgery without severe cognitive impairment prior to surgery are included. PHQ-9 (Patient Health Questionnaire) scores will be collected pre- and post-surgery as a surrogate measure for depression and compared between both allocation groups. A linear mixed model will be used to measure change in PHQ-9 scores after 3 months.

Results: The sub-study explores the relationship between PHQ-9 scores (depression surrogate) and exposure to dexmedetomidine after open-heart surgery. Across CODEX's participating sites, 540 consented (362 enrolled, 178 excluded, pending surgery, or pending baseline assessment) to the larger CODEX study. Participants with pre-existing cognitive impairment, an aortic arch replacement, or contraindication to dexmedetomidine were not included in the study. Of enrolled participants, 362 completed the PHQ-9 at baseline and 288 completed the 3-month follow-up assessment as of January 2025.

F.3: Sex differences in neuropsychiatric symptoms associated with agitation in frontotemporal lobar degeneration

Student: Celine Sakran, Supervisor: Carmela Tartaglia

Background: Agitation is a clinically significant symptom contributing to behavioral and psychological symptoms of dementia (BPSD), but is poorly understood across the different syndromes related to Frontotemporal Lobar Degeneration (FTLD). Agitation frequently coexists with various neuropsychiatric symptoms (NPS), and leads to increased level of impairment, caregiver burden and distress, risk of institutionalization and poorer clinical outcomes.

Purpose and Hypothesis: This study investigates sex differences in agitation-related NPS in FTLD-related syndromes. We hypothesize that males and females exhibit distinct NPS profiles in association with agitation.

Methods: We analyzed data from 1,654 participants (916 males, 738 females; mean ages 65.8 and 65.9, respectively) from the National Alzheimer's Coordinating Center (NACC) and ARTFL-LEFFTDS Longitudinal FTLD (ALLFTD) study. Participants were diagnosed with behavioral variant FTD (bvFTD), non-fluent (nfvPPA) and semantic (svPPA) variants of Primary Progressive Aphasia, Corticobasal Syndrome (CBS), or Progressive Supranuclear Palsy (PSP). The Neuropsychiatric Inventory (NPI) assessed agitation and NPS. Prevalence and odds ratios determined sex differences in NPS when agitation was present. Principal Component Analysis (PCA) identified symptom clusters.

Results: Males with agitation were more likely to experience anxiety (bvFTD: $p<0.001$, CBS: $p<0.01$, PSP: $p<0.0001$), apathy (nfvPPA, PSP: $p<0.01$), depression (bvFTD: $p<0.0001$, PSP: $p<0.01$), disinhibition (nfvPPA: $p<0.0001$, PSP: $p<0.001$), and motor symptoms (bvFTD, CBS: $p<0.01$). Females had a higher likelihood of disinhibition in svPPA ($p<0.001$). Males with PSP exhibited the widest range of NPS associated with agitation.

Conclusions: Agitation in FTLD-related syndromes is linked to distinct NPS profiles by sex, with males experiencing a broader spectrum of symptoms. These findings emphasize the importance of sex-specific research into the neurobiological and informant-related factors influencing symptom presentation and recognition, ultimately improving agitation management and BPSD in FTLD.

F.4: Association of clinical and electrophysiological biomarkers of upper and lower motor neuron dysfunction with neurofilament light chain levels in amyotrophic lateral sclerosis

Student: Denizart Santos Neto, Supervisor: Lorne Zinman, Agessandro Abrahao

Background: Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease with heterogeneous clinical presentations involving both upper (UMN) and lower motor neuron (LMN) dysfunction. Neurofilament light chain (NfL) has emerged as a promising biomarker in ALS, with diagnostic, prognostic, safety, and risk applications. Although NfL is associated with disorders of both the central and peripheral nervous systems, its primary source in ALS remains unclear.

Purpose and Hypothesis: Our study aimed to explore serum NfL variability in patients with ALS in relation to clinical and electrophysiological measures of upper and lower motor neuron dysfunction. We hypothesized that clinical and electrophysiological markers of UMN and LMN dysfunction are associated with NfL levels after adjusting for covariates (sex, age, and site of onset) and including interaction terms involving the ALS Functional Rating Scale – Revised (ALSFRS-R) score, its rate of decline, and disease duration.

Methods: A cross-sectional analysis was conducted using baseline data from 47 participants in the NiALS study (Nuclear Factor Kappa Beta Inhibition in Patients with Amyotrophic Lateral Sclerosis). Clinical measures included the Pennsylvania Upper Motor Neuron Score (PUMNS) and Devine's LMN score. Neurophysiological assessments comprised Resting Motor Threshold (RMT), Compound Muscle Action Potential (CMAP), Motor Unit Number Index (MUNIX), and Strength-Duration Time Constant (SDTC). Linear models were used to assess associations between NfL levels and these measures, while controlling for covariates and interaction terms.

Results: NfL levels were inversely associated with ALSFRS-R scores ($p < 0.001$) and positively associated with both the ALSFRS-R decline rate ($p < 0.001$) and PUMNS ($p = 0.002$). Although RMT and SDTC showed no overall association with NfL, both became significant when adjusted for disease duration (RMT, $p = 0.03$; SDTC, $p = 0.008$). LMN score, CMAP, and MUNIX were not significantly associated with NfL.

Conclusions: Our findings suggest that both LMN and UMN pathology influence NfL levels after adjusting for covariates. However, ALS-related variability appears more strongly associated with UMN dysfunction, as indicated by significant associations with clinical and electrophysiological markers of UMN involvement.

F.5: Theta-gamma phase-amplitude coupling in the dynamic pain connectome in healthy individuals and abnormalities in people with chronic pain

Student: Ariana Seyed Makki, Supervisor: Karen Davis

Background, Purpose, and Hypothesis: How does the brain process nociceptive stimuli and contribute to chronic pain? Phase-amplitude coupling (PAC) of neural oscillations is involved in encoding and parsing of sensory inputs as well as neural communication and coordination in the brain. Theta-gamma PAC, in particular, could serve to gate nociceptive processing and modulation at different points of interaction within the dynamic pain connectome (DPC). This study investigated whether there is normally theta-gamma PAC of intrinsic activity within the DPC and whether it is disrupted in people with chronic pain. We hypothesize that theta-gamma PAC is present in key nodes of the DPC in healthy and chronic pain states and that it exhibits abnormalities in chronic pain.

Methods: Resting-state magnetoencephalography was used to measure theta-gamma PAC in 38 healthy individuals (20 M, 18 W) and 37 individuals with chronic pain associated with ankylosing spondylitis (20 M, 17 W). The magnitude and incidence of PAC was assessed in nodes of the ascending nociceptive and descending antinociceptive pathways, default mode and salience networks. We also examined whether there were associations between PAC and each patient's chronic pain intensity, disease severity, and functional limitations.

Results: Most or all individuals in the healthy and chronic pain groups exhibited PAC in all DPC regions tested, except the subgenual anterior cingulate cortex of the descending antinociceptive pathway (37% and 45%, respectively). Individuals with chronic pain exhibited PAC abnormalities in the right midcingulate cortex of the salience network, which also had moderate associations with disease severity and functional limitations. Compared to males, females with chronic pain showed more widespread PAC abnormalities across the DPC.

Conclusions: This study provides novel data to implicate theta-gamma PAC as a means to shape the outcome of noxious input to the brain. These findings also point to PAC failures as a possible abnormality that could contribute to chronic pain.

F.6: Neurobiological mechanisms of stress susceptibility and resilience: Whole-brain structural covariance network analysis

Student: Rubab Shafiq, Supervisors: Yuliya Nikolova

Background: Chronic stress is a major risk factor for many psychiatric illnesses. Some individuals are more susceptible to stress than others; however, the mechanisms underlying this inter-individual variability remain unclear. Prior research has identified neuroanatomic differences in brain structures that mediate stress susceptibility. Here, we use structural brain imaging and graph theory metrics to reveal whole-brain synchronized volumetric changes associated with stress susceptibility and resilience in mice.

Purpose: This study aims to investigate structural covariance network differences associated with stress susceptibility and resiliency.

Hypothesis: We hypothesize that stress resilient mice will be associated with structural covariance network differences through a loss of modularity.

Methods: Adult male mice (8 weeks old) underwent a social defeat stress paradigm and were tested for social avoidance. Mice with social interaction ratios <1 were classified as susceptible and those >1 as resilient. Following ex-vivo T2-weighted MRI, volumes from 154 regions were extracted using deformation-based morphometry. Structural covariance networks (SCN) were modeled using the *igraph* package in R. Pair-wise group differences among resilient (n=8), susceptible (n=11) and control (n=12) mice, were used to analyze region-specific hubness (degree centrality), whole-brain network integration (mean distance), and segregation (modularity) across network density thresholds (5-40%). Significance was tested using 1,000 permutations.

Results: Resilient mice had significantly lower modularity, compared to both control and susceptible mice ($p<0.05$, 8 network densities). Susceptible mice had lower thalamus degree centrality, relative to resilient mice ($p<0.05$, densities 8-11%), whose thalamic degree was comparable to that of controls.

Conclusions: Our findings suggest that lower SCN modularity, indicative of reduced local network specialization and a shift toward a more integrated network, may be a marker of stress resilience, while reduced thalamic hubness may be a marker of susceptibility.

F.7: Utilization of emergency department services among children with neurodevelopmental diagnoses: A scoping review

Student:Humna Siddiqui, Supervisor: Melanie Penner

Background: Children with neurodevelopmental diagnoses (NDDs) have complex healthcare needs which are often not adequately addressed due to the lack of suitable services. As a result, they rely heavily on emergency departments (EDs). The chaotic ED environment can be challenging for children with sensory/ behavioural issues, leading to heightened stress. A significant gap in the knowledge, experience, and training of ED staff regarding the care of neurodivergent patients only further exacerbates barriers to accessing quality care. Existing reviews focus on a single NDD, often overlooking these conditions' shared features and frequent co-occurrence.

Purpose and Hypothesis: This scoping review aims to examine the extent of the literature for various NDDs related to ED utilization, identify common behavioural presentations to the ED, and highlight challenges faced by children with NDDs in this setting.

Methods: A systematic search across Embase, PSYCHINFO, MEDLINE, Web of Science, and CINAHL included original, peer-reviewed articles on hospital ED usage among children with NDDs. Two reviewers screened 5434 abstracts and 581 full texts, yielding 47 studies for inclusion.

Results: Behavioural presentations to the ED included down syndrome, autism spectrum disorder (ASD), attention-deficit/hyperactivity disorder (ADHD), and intellectual disability., with ASD and ADHD presenting most commonly (67% of studies). Reasons for visits included physical injuries from attempted suicide, bone fractures, constipation, psychiatric hospitalizations, and non-traumatic dental conditions. Two studies highlighted increased sedation and restraint use among children with NDDs. In one study, over 25% of sedations were for non-invasive procedures (e.g., routine physical exams), with 10% receiving neuroleptics (e.g., haloperidol or olanzapine), typically uncommon for such procedures. Another study reported significantly higher odds of restraint use among children with ASD (aOR 2.9) and ADHD (aOR 2.2). These findings highlight sedation and restraint as barriers to care in ED settings.

Conclusions: Frequent ED use by children with NDDs suggests it is often a primary point of care, underscoring the need to equip ED staff with the proper training/ tools to address the unique needs of each child. Addressing ED challenges and enhancing staff knowledge are critical to establishing equitable care frameworks and ensuring tailored, comprehensive care for children with NDDs.

F.8: Association between glycemic control and accelerated rTMS efficacy in treatment-resistant depression: An interleaved rTMS-fMRI study

Student: Dara Silver, Supervisor: Sean Nestor

Background: Major depressive disorder (MDD) is a debilitating disorder that affects millions of individuals worldwide. Approximately 30% of individuals have treatment-resistant depression (TRD) and do not respond to first-line treatments. Repetitive transcranial magnetic stimulation (rTMS) is an established, non-invasive treatment for MDD. It uses rapidly changing magnetic fields to induce electrical currents in targeted brain regions, which can modulate neuronal activity, connectivity and plasticity. Up to half of patients with TRD do not achieve response or remission with rTMS protocols.

Metabolic dysfunction has been associated with major depressive disorder (MDD) and is 2-3x more prevalent in persons with metabolic dysfunction. There are no studies that have evaluated how rTMS response is associated with glucose metabolism. It has not been examined whether impaired glucose regulation in a non-diabetic population is associated with decreased response to rTMS. Identifying biomarkers such as glucose dysfunction could provide valuable insights for predicting and enhancing rTMS treatment outcomes. To our knowledge, this study is the first to investigate the association between glucose control measures and rTMS efficacy in TRD.

Objective and Hypothesis: This study aims to evaluate the relationship between rTMS efficacy and metabolic dysfunction in individuals with MDD, with a particular focus on measures of glucose control. We hypothesize that poor glucose control (i.e., higher fasting blood glucose, glycated hemoglobin (HbA1c)), which may reflect underlying metabolic or inflammatory dysfunction, will be associated with decreased therapeutic efficacy of rTMS.

Methods: Participants were prospectively recruited from an ongoing open-label trial of connectivity-guided, accelerated intermittent theta burst stimulation (iTBS) rTMS at Sunnybrook Health Sciences Centre. Eligibility criteria include adults with treatment-resistant depression who meet the inclusion criteria of the ongoing trial. Patients received 8 daily sessions of iTBS consecutively for 5 days, targeting the left dorsolateral prefrontal cortex using image-guided neuronavigation. The primary outcome measures were change on the Montgomery-Asberg Depression Rating Scale (MADRS) scores assessed at day 5 and a 4-week follow-up to evaluate both immediate and sustained treatment effects. Blood measures included fasting glucose and HbA1c collected one week before iTBS treatment. Linear regression analysis was used to examine the association between baseline glucose measures and changes in MADRS scores.

Results: 30 participants aged 20-65 with a diagnosis of TRD were included. No significant correlation was observed between baseline HbA1c and MADRS scores (on day 5 n=29, r=-0.1, p=0.59; at week 4 n=24 r=0.04, p=0.86) or between FG and MADRS (day 5 n=28 r=-0.20, p=0.3; week 4 n=24, r=-0.03, p=0.90).

Conclusion: Long-term glucose markers were not found to be associated with greater improvement in depressive symptoms. Future work will explore insulin levels and more detailed measures of insulin variability in relation to rTMS, which are more sensitive markers of metabolic dysfunction in persons without pre/diabetes.

G: Neuroscience & Brain Health

G.1: Effects of theta-burst transcranial ultrasound stimulation on cerebral blood flow, functional connectivity, and working memory performance in Parkinson's disease

Student: Kiah Spencer, Supervisor: Robert Chen

Background: Working memory (WM) decline is a common experience for patients with Parkinson's disease (PD) and is associated with worsened prognosis. The frontoparietal network (FPN) is crucial for WM and coordinating goal-oriented behaviour. Within the FPN network, the left dorsolateral prefrontal cortex (L DLPFC) is especially relevant for WM and is impacted by PD. Neuroimaging studies using resting-state functional magnetic resonance imaging (rsfMRI) and arterial spin labelling (ASL) have demonstrated that PD patients show reduced frontoparietal network (FPN) functional connectivity (FC) and cerebral blood flow (CBF), and this hypoactivity correlates with worsened WM performance on N-back tasks. Transcranial ultrasound stimulation (TUS) is a non-invasive, spatially precise neuromodulation technology that can penetrate deep brain structures affected by PD. As TUS is a new technology, its neuromodulatory effects are still an area of active investigation. Our lab recently applied tbTUS to the L DLPFC in healthy young adults and found increased WM performance under conditions of high cognitive load (2 and 3 back conditions), accompanying increased DLPFC excitability. To extend these findings, we propose the following

Objectives: 1. investigate the effects of tbTUS on WM load (1-2-3-back) using the N-back task in PD patients, and 2. implement the above neuroimaging modalities as a functional readout of tbTUS' effects.

Outcome measures: N-back overall accuracy (1-2-3 back), post-tbTUS FC in the L DLPFC and FPN, and post-tbTUS CBF in the L DLPFC and FPN.

Hypotheses: 1. tbTUS to L DLPFC will enhance WM performance in 2 and 3 back conditions; 2. Enhanced WM performance will correlate with increased DLPFC and FPN activity post-sonication.

Methods: We will recruit 15 PD patients and 15 healthy controls (HCs). To control for age-related structural changes, we will only recruit participants between ages 60 and 75. HCs will have one visit, during which they will complete the N-back task and undergo an anatomical MRI (T1 & T2), rsfMRI, and ASL. Patients will complete three visits ON medication. The first will involve an anatomical MRI (T1 & T2). We will conduct offline TUS modelling between visits 1 and 2 to obtain ultrasound parameters based on individual anatomy and to ensure safe and accurate DLPFC sonication. Visits 2 and 3 are identical, except the sonication condition (active or sham) will be randomized. Patients will complete baseline clinical (MDS-UPDRSIII) and N-back assessment, undergo baseline rsfMRI and ASL, neuro-navigation guided tbTUS to L-DLPFC (active/sham, randomized) for 120 s, post-rsfMRI and ASL, and post clinical and N-back assessment.

Expected results: Our previous lab work using tbTUS on the L DLPFC showed a neuromodulatory effect. We expect this neuromodulatory effect to occur in the FPN network. Since hypoactive FC between the DLPFC and other FPN structures correlates with worsened WM performance in 2 and 3 back tasks, we expect at post sonication patients who show a higher degree of increased FPN FC will have higher accuracy in 2 and 3 back tasks than patients who do not. We also expect increased FC to coincide with increased DLPFC and FPN CBF.

Significance: Worsened cognition is associated with increased falls, hospitalization, and caregiver burden. As of 2010, approximately 31.3% of PD patients have dementia, and of the general PD population, around 10% develop dementia annually. Neural areas relevant to cognition decline before patients notice- and eventually, one of the first noticeable symptoms is memory decline. Therefore, it is of utmost importance to provide early intervention. Indeed, cognitive symptoms are notoriously hard to treat due to varying aetiologies. If tbTUS to the DLPFC in PD shows promise in improving WM and altering the

pathophysiological neural circuitry responsible for WM deficits, it can be further developed into a novel treatment for PD patients with mild cognitive impairment and dementia.

G.2: Free-water diffusion and quantitative T1 mapping in FTLD

Student: Vishaal Sumra, Supervisors: Maria Carmela Tartaglia

Introduction: Neuroinflammation has been proposed as a common feature of neurodegenerative diseases (NDs). Differences in inflammatory profiles have been observed between NDs suggesting disease specific inflammatory profiles. In frontotemporal lobar degeneration (FTLD), neuroinflammation and proteinopathy are expected in frontal and temporal regions, depending on subtype. Free-water diffusion (FWD) and T1 maps are non-specific biomarkers of neuroinflammation, where increased tissue water caused by cytokine release is expected to increase both FWD and T1 values. Here we investigate T1 mapping and FWD as candidate neuroinflammatory biomarker in FTLD.

Methods: Data was acquired in 25 subjects: 8 corticobasal syndrome (CBS, 4M 4F, mean age 65), 3 semantic variant primary progressive aphasia (svPPA, 3F, mean age 80), 4 progressive supranuclear palsy (PSP, 3F, 1M mean age 77), 7 behavioural variant frontotemporal dementia (bvFTD) (6M,1F mean age 68), and 3 healthy control subjects with a family history of FTLD but gene negative (1M,2F, mean age 52). T1-weighted MPRAGE, diffusion-weighted EPI (two shells) for free-water mapping, and MP2RAGE for qT1 mapping were acquired on a Siemens MAGNETOM Prisma 3T scanner. Skull stripping and binary mask creation were done using ICVmapp3r on T1-weighted MPRAGE scans. MP2RAGE T1 maps were corrected for B1+ using a separately acquired B1+ map. FWD maps were processed with Synbo, FSL's topup, FSL's eddy, and in-house MATLAB to generate final FWD maps. FWD and T1 maps were co-registered using FSL flirt. FWD and T1 values were extracted in the caudate, as well as frontal and temporal regions where FTLD pathology is expected.

Results: FWD maps show good contrast between tissue and CSF, whereas T1 maps show good contrast between grey matter, white matter and CSF. We observe trends in the expected directions with increased T1 and FW in frontal vs occipital regions in PSP, bvFTD, CBS and svPPA patients, and increased FW and T1 in the frontal cortex in bvFTD, CBS, and PSP patients compared to clinically normal individuals.

Discussion: Our preliminary results suggest that both FWD and qT1 are increased in areas where pathology is expected in FTLD syndromes. Further studies will as examine the relationship between FWD, qT1 and biofluid based neuroinflammatory biomarkers.

G.4: Brain insulin signaling modulates effort allocation in mood disorders: Impact of reward magnitude, reward probability, and depression severity

Student: Aniqa Tabassum, Supervisor: Rodrigo Mansur

Background & Purpose: Mood disorders (i.e., major depressive disorder (MDD) and bipolar disorder (BD)) and metabolic disorders (e.g., type-2 diabetes (T2D)) have a bidirectional epidemiological association. To uncover mechanisms underlying the mood-metabolic disorders comorbidity, this randomized, double-blind, placebo-controlled, crossover trial is investigating the role of brain insulin signaling and peripheral insulin resistance (IR) in effort-based reward behaviour in individuals with mood disorders compared to healthy controls (HCs).

Hypotheses: This study hypothesizes that compared to healthy individuals, individuals with mood disorders will show a decreased willingness to exert effort for reward and reduced cortico-striatal insulin response.

Methods: This preliminary analysis assessed effort-based decision-making in 44 subjects (19 BD, 22 MDD, 3 HCs) using the Effort-Expenditure for Rewards Task (EEfRT) in a functional MRI paradigm after intranasal insulin and placebo administration. Peripheral IR was calculated using the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR).

Results: There was no significant main effect of treatment condition in the sample ($p=0.257$) on overall effort expenditure for reward. However, significant interaction effects between condition and reward magnitude ($F=32.1$, $p<0.001$) as well as probability ($F=10.9$, $p<0.001$) moderated mean proportion of hard task choices indicating that insulin administration affects effort allocation depending on magnitude and probability of reward. Depression score on the Montgomery Åsberg Depression Rating Scale (MADRS) also had a moderating effect on choice ($F= 4.8$, $P=0.029$). There were no significant moderating effects of age, sex, diagnosis, peripheral IR, or visit number on mean proportion of hard task choices in the overall sample.

Conclusions: The findings suggest a role of brain insulin action on efficiently allocating effort to maximize rewards. The data collected from fMRI is expected to elucidate potential underlying differences in brain activity.

G.5: Focused ultrasound modulation of cerebellar inhibition

Student: Huseyin Taskin, Supervisors: Robert Chen

Background: The cerebellum inhibits the primary motor cortex (M1), a key mechanism for motor learning and precision. This inhibition is typically measured non-invasively using a transcranial magnetic stimulation (TMS) protocol, where a TMS pulse to M1 elicits motor-evoked potentials (MEP) in hand muscles, and a preceding cerebellar pulse reduces MEP amplitude. While cerebellar lobules V and VIII are thought to be involved in this inhibition, TMS lacks the focality to isolate their individual contributions, as it activates a large portion of the cerebellar cortex. Transcranial ultrasound stimulation (TUS), a novel neuromodulation technique that uses ultrasound waves to modulate neuronal activity, offers deeper and more focal stimulation than TMS, making it a promising tool for cerebellar functional mapping.

Purpose and Hypothesis: This pilot study assessed whether TUS can modulate M1 excitability via cerebellar stimulation. We hypothesized that TUS targeting lobules V and VIII would decrease M1 excitability, whereas TUS targeting the dentate nucleus, a primary cerebellar output region with excitatory projections to the cortex, would increase M1 excitability.

Methods: The M1 hand region was identified with TMS, and baseline MEP amplitude was recorded by averaging responses from 20 pulses. TUS (PRF = 1000Hz, duty cycle = 10%) was applied to lobules V, VIII, and the dentate nucleus for 0.5 s, with TMS pulse delivered to M1 0.45 s into ultrasound stimulation. Each cerebellar site was stimulated 20 times with 5-second intervals. Sham conditions included (1) TUS applied to V1, (2) zero-watt TUS, and (3) TUS with the transducer flipped away from the head.

Results: On average, MEP amplitude ratios (paired TUS-M1 vs. baseline) showed inhibition for lobule V (0.54 ± 0.23) and lobule VIII (0.44 ± 0.19), while dentate sonication showed excitation (1.38 ± 1.25). However, dentate excitation was present only in two subjects, while the remaining two exhibited inhibition. The reason for this inconsistency could be due to TUS hitting inhibitory white matter pathways entering the dentate in these subjects. The sham conditions yielded values similar to baseline (V1: 1.02 ± 0.40; zero-watt: 1.26 ± 0.46; flipped transducer: 1.23 ± 0.25).

Conclusion: These initial findings suggest that both lobule V and VIII contribute to cerebellar inhibition of M1 and demonstrate the potential of TUS for selective stimulation of cerebellar lobules. The main study will refine targeting and investigate variability in dentate responses.

G.7: Functionally-informed polygenic risk scores for schizophrenia and antipsychotic response

Student: Megana Thamilselvan, Supervisor: Jim Kennedy

Background: Schizophrenia (SCZ) is a debilitating mental illness, and it is mainly treated with antipsychotics (APs). AP response is variable, with only about 40% of patients experiencing an improvement in symptoms. Treatment efficacy can be increased by predicting outcomes using genomic tools and personalizing treatment accordingly. Polygenic risk scores (PRS) are valuable tools for studying polygenic traits such SCZ and AP response. A PRS is calculated as the weighted sum of all SNPs affecting the trait. SCZ, bipolar disorder (BPD) and major depressive disorder (MDD) PRSs have all been previously associated with SCZ symptoms/diagnosis and AP response. Here, we studied a gene expression risk score (GeRS), a type of PRS that weights genes by their expression levels in the tissue of interest, providing a functionally-informed score.

Purpose and Hypothesis: We investigated the association between GeRS and SCZ case/control status, as well as response to APs. We compared the total variance in each outcome (R^2) explained by GeRS versus a standard PRS. We hypothesized that SCZ, MDD and BPD GeRS would be associated with SCZ diagnosis, and SCZ and antidepressant response (ADR) GeRS would be associated with AP response.

Methods: Using GWAS summary statistics for SCZ, MDD, BPD and ADR, a FUSION transcriptome-wide association study (TWAS) was done to establish gene expression-trait correlations. ADR GWAS was selected due to the lack of a well-powered AP response GWAS, and shared pathways between AD and AP action. Individual-level genotypes from the IMPACT (n=3377) and CATIE (n=322) cohorts were obtained and gene expression was imputed to calculate GeRS. Logistic and linear regression models were used to respectively evaluate GeRS as predictors for SCZ diagnosis (IMPACT) and ΔPANSS score (a psychiatric scale used to assess symptoms) after 6 months of AP treatment (CATIE). FDR correction was applied. PRS were calculated using the standard p-value and clumping thresholding method for comparison.

Results: SCZ GeRS was significantly associated with SCZ diagnosis (Nagelkerke R^2=0.098, p=0.008). This corroborates findings from previous studies. ADR GeRS was nominally associated with ΔPANSS score (R^2=0.155, uncorrected p=0.056). This points to the shared action of APs and ADs in the brain, and ADR GWAS may serve as a valuable alternate source of information in the absence of a robust AP response GWAS. GeRS had marginally higher R^2 than PRS when predicting AP response (ΔR^2=0.006), but lower for SCZ diagnosis (ΔR^2=0.06). The effect size of the GeRS in all models was modest.

Conclusions: There is a significant association between SCZ GeRS and SCZ diagnosis, and a nominal association between ADR GeRS and AP response. For predicting SCZ diagnosis, a standard PRS explains more variability than GeRS. However, GeRS provides a marginal increase in R^2 compared to PRS for AP treatment outcome. This study is limited by a small sample size for studying AP treatment outcomes, and replication in a larger cohort would confirm the validity of the findings.

G.8: Using smartphone technology to detect mood episodes and symptoms in young individuals living with bipolar disorder

Student: Hannan Ullah, Supervisor: Stefan Kloiber, Jacob Vorstman

Background: Clinical evidence suggests that early symptoms precede mood episodes in bipolar disorder (BD), but high individual heterogeneity and a lack of common prodromes challenge early detection of relapse. The ubiquity of smartphones in daily life has led to the emergence of passive monitoring — real-time, real-world data collection using smartphone applications and wearable devices — to derive objective digital behavioural markers in individuals with BD.

Purpose: Using BEHAPP, a smartphone-based passive monitoring software, we aim to study possible behavioural differences between euthymic and mood episode states, and whether early changes leading up to a mood episode relapse can be identified.

Hypothesis: Behavioral data patterns can differentiate between healthy and mood episode states and early changes in behavioural patterns during prodromes of mood episodes can be detected in smartphone-derived data.

Methods: We initiated an observational study with BEHAPP installed on participants' personal smartphones (target n = 100) to passively collect behavioural data over 12 months. Symptoms of depression and mania were evaluated through repeated completion of the Patient Health Questionnaire-9 (PHQ-9) and Altman Self-Rating Mania Scale (ASRM). Presence of BD and mood episodes were identified using the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (SCID-5) at baseline, 6 and 12 months at-minimum and following a change in mood symptoms based on PHQ-9 and ASRM scores. The relationship between smartphone-derived data and prodromal mood symptoms was quantified using a linear mixed-effects model.

Results: 27 participants have been enrolled; 14 participants have completed the six-month visit. Preliminary analysis indicated that reduced activity levels and decreased social communications predicted greater levels of depressive symptoms, as reflected by increased duration spent still (β = 21.76; p = 0.005) and fewer incoming calls (β = -0.70; p = 0.050), respectively. Manic symptoms were associated with increased activity levels and fewer places visited, indicated by reduced time spent stationary (β = -0.21; p = 0.009) and reduced staypoints (β = -0.12; p = 0.022).

Conclusions: The urgency and significance of this work is demonstrated by detrimental social and occupational disruptions associated with mood episodes relapse and the fact that BD, among psychiatric disorders, has the highest suicide rate. This project is novel and will help advance our understanding of passive monitoring data in relation to mood states in BD, which is essential for creating a tool to facilitate early mood episode detection and recognition. We demonstrate the feasibility of enrollment, study procedures, and detecting behavioural changes using smartphone data. Data collection is ongoing and will allow us to examine whether smartphone-based passive monitoring has the potential to facilitate early detection and recognition of mood episodes, opening doors for early intervention, and possibly, prevention.

H: Neuroscience & Brain Health

H.1: AI conversational agent to improve varenicline adherence: A mixed methods feasibility study

Student: Sidra Anjum, Supervisor: Nadia Minian

Background: Tobacco use remains the leading preventable cause of death in Canada, resulting in approximately 46,000 deaths annually. Smoking cessation significantly reduces the risk of smoking-related health complications, with varenicline being the most effective pharmacological treatment. However, over 30% of individuals prescribed varenicline are non-adherent by the second week, reducing the likelihood of successful cessation. Current interventions for improving adherence are often complex and costly, leaving a critical gap in treatment implementation. The Centre for Addiction and Mental Health, the University of Toronto, and Memotext developed an artificial intelligence (AI) chatbot, ChatV, that aims to increase adherence to varenicline through delivering personalized support, tracking medication adherence, offering timely reminders, and engaging in motivational conversations.

Purpose and Hypothesis: This study aims to explore the feasibility of an AI chatbot, to examine if it is used as intended, and to determine the appropriateness of proceeding with a randomized controlled trial. I hypothesize that the chatbot will improve medication adherence.

Methods: 40 participants will be prescribed a 12-week varenicline regimen and engage with the AI chatbot throughout the study. Surveys will be administered at weeks 1, 4, 8, and 12 to assess smoking status and medication adherence. At the end of the study, participants will participate in a one hour interview to explore their experiences with the chatbot.

Results: This study aims to provide valuable insights into the use of AI chatbots for medication adherence and promote smoking cessation. Findings will inform future research and have the potential for broad implementation in primary care and addiction treatment settings.

H.2: Chronic condition status is associated with self-harm in children

Student: Matisse Blundell, Supervisor: Jacob Vorstman, Suneeta Monga

Background: Deliberate self-harm has increased dramatically among Ontario children, with rates of Emergency Department (ED) presentations for this indication doubling since 2009. Self-harm is typically considered to refer to deliberate physical self-injury in the absence of suicidal intent. A broader conceptualization, which will be used here, includes behaviors with at least some degree of suicidal intent. Children presenting to the ED for a first episode of self-harm are at high risk of repeat self-harm and death by suicide. Understanding risk factors for these adverse outcomes may inform assessment and treatment.

One potentially relevant risk factor to consider is history of chronic health conditions. Children with chronic mental health conditions are at higher risk of initiating self-harm, and of repeating self-harm following a first episode. Less is known about the potential effect of chronic health condition history more broadly, i.e. including chronic physical health conditions such as diabetes or asthma. Previous retrospective studies indicate that youth who die by suicide are twice as likely to have had a chronic physical health condition. It is unclear whether a history of chronic condition(s) is associated with initial or repeat self-harm.

Purpose and Hypothesis: This study leveraged population health data to examine potential associations between a history of any chronic condition(s) and self-harm in children. We hypothesized that: 1) Compared to the general population, children presenting to the ED for first-time self-harm are more likely to have a history of chronic condition(s), and 2) Chronic condition status at the time of first presentation with self-harm can be associated with the probability of subsequent re-presentation(s) for self-harm.

Methods: We obtained healthcare administrative data from ICES (formerly the Institute for Clinical Evaluative Sciences). ICES houses de-identified, individual-level data on all hospital encounters and outpatient physicians' services in Ontario. We included all children aged 8-17 years who made a first-time ED presentation for self-harm between 2013-2022 ("cases"). Each case was matched to up to 5 controls presenting to the ED for other reasons by age, sex, and socioeconomic status (income quintile and urban/rural residence). Chronic condition status was measured using the pediatric adaptation of the AHRQ Chronic Conditions Indicator, provided by Boston Children's Hospital in advance of public release. We used this indicator to identify children with a history of hospitalization for any chronic condition since 1 year of age. In a sub-analysis, we identified children with a history of hospitalization for a chronic physical condition.

Results: We identified 26 857 cases and 112 376 controls. The majority of cases were female (77.5%) and the mean age at first presentation for self-harm was 14.98 ± 1.68 years. Cases were relatively evenly distributed by income quintile (19-22% per quintile) and the majority were urban-dwelling (85.0%). History of any chronic condition was recorded for 34.1% of cases compared to 10.4% of controls. When excluding mental health-related hospitalizations, 19.8% of cases compared to 10.2% of controls had a history of chronic physical health condition.

Conclusions: Compared to matched controls, a higher proportion of children presenting to an ED with first-time self-harm have a history of (1) any chronic condition and (2) a chronic physical health condition. The population of children with chronic conditions may represent a high-risk group where preventative interventions for self-harm could be targeted. Further research will investigate the predictive value of chronic condition status for repeat self-harm.

H.3: Feasibility, implementation, and real-world effectiveness of repetitive transcranial magnetic stimulation for tobacco smoking cessation

Student: Alexandra Sas, Supervisor: Nadia Minian, Victor Tang

Background: Repetitive transcranial magnetic stimulation (rTMS) is a novel, non-invasive and safe smoking cessation treatment for daily cigarette smokers. This intervention was FDA approved based on trials that excluded patients with mental illness, however it is unclear whether this intervention would be equally feasible and acceptable in real-world settings that include such patients.

Purpose, Methods and Hypothesis: We aimed to evaluate the feasibility and acceptability of rTMS for smoking cessation by surveying 62 patients recruited from a real-world smoking cessation clinic based out of the Centre for Addiction and Mental Health. A subgroup of 13 patients enrolled to receive the treatment; we hypothesized that at least 70% would complete treatment.

Results: The average age of the 64 participants was 50.5 (± 12.4) and 45.3% had a mental illness, primarily depression and anxiety. The Acceptability of Intervention Measure showed that 81.8% agreed that the treatment was appealing and 63.6% agreed the time commitment was acceptable. The maximum time participants were willing to travel for this intervention was 48 (± 28) minutes; however, 46.9% reported that travel costs were likely unaffordable. Out of 13 patients who enrolled in treatment, 9 completed treatment, 1 withdrew during treatment, 3 withdrew before treatment. One person reached abstinence by the end-of-treatment.

Conclusions: There was high interest among smoking cessation patients in rTMS as a treatment option, but time and travel commitment were common access barriers. Most of the patients who started rTMS completed the full regimen. Many real-world smokers present with medical and psychiatric complexity therefore researching implementation barriers is needed to inform the integration of rTMS in routine clinical care.

H.4: The role of the FREM3 gene in synaptic density network integration and segregation measured by PET imaging

Student: Priya van Oosterhout, Supervisor: Yuliya Nikolova

Background: The human FREM3 gene has become a target of interest for its hypothesized role in neuroplasticity, and the potential role of FREM3-expressing excitatory neurons in long-range connectivity. Structural covariance networks (SCNs) measure morphological synchronization across brain regions and may serve as a proxy for whole-brain patterns of inter-regional connectivity and shared plasticity. To provide insight into the effects of FREM3 on whole-brain organization, we applied SCN modeling to regional synaptic density PET imaging data acquired from a novel excitatory-neuron-specific Frem3-knockout (Frem3-enKO) mouse model.

Purpose: To determine the effect of the FREM3 gene on whole-brain organization and connectivity via a synaptic density covariance network.

Hypothesis: FREM3 knockout will be associated with increased network modularity (greater segregation) and decreased network integration (greater mean distance between nodes), indicative of decreased global connectivity and efficiency.

Methods: PET imaging with [^{18}F]SynVesT-1 was used to measure regional levels of synaptic vesicle glycoprotein 2A (SV2A) as a proxy for synaptic density in 3-month-old Control (CT, n=8, 50% female) and Frem3-enKO (n=6, 50% female) mice. Regional volume of distribution (V_T) was estimated for 21 bilateral regions using Logan's plot, t*=30, with image derived input function from left ventricular blood pool. After regressing out the effects of sex, SCNs were generated using the R package 'igraph'.

Results: Graph theory metrics of network integration (mean distance) and segregation (modularity) were assessed across network densities (5%-30%), using 2000 permutations. Frem3-enKO mice had markedly higher network modularity and greater mean distance, relative to CT mice ($p<0.05$, densities: 5-30%, and 16-24%, respectively), indicative of greater network segregation and lower integration. Our findings suggest that excitatory neuronal Frem3 is critical to whole-brain network integrative capacity.

Conclusions: This preliminary study is consistent with the hypothesized role of FREM3-expressing excitatory neurons in mediating long-range connectivity in the human brain and supports the translational validity of our model.

H.5: Indicators of major depressive disorder (MDD) subgroups within the major depressive disorder integrated care pathway (MDD-ICP)

Student: Siya Verma, Supervisor: Stefan Kloiber

Background: Individuals with Major Depressive Disorder (MDD) experience reduced life expectancy, lower quality of life, and an increased risk of comorbid psychiatric and physical illnesses. Currently, the effectiveness of MDD treatments is limited, with initial remission rates only around 30%. The MDD-ICP at CAMH utilizes measurement-based care to deliver structured, iterative treatment. Clinical and biological heterogeneity among individuals with Major Depressive Disorder (MDD) contributes to outcome variability and remains underexplored, limiting treatment effectiveness.

Purpose and Hypothesis: This study aims to identify distinct subgroups within adults with MDD by examining demographic, behavioral, clinical, and biological factors including actigraphy-derived data in conjunction with analyzing treatment outcomes in order to inform individualized care strategies. We hypothesize that data will reveal subgroups or sub-phenotypes within MDD.

Methods: This longitudinal observational study aims to recruit 100 adults diagnosed with major depressive disorder from the MDD Integrated Care Pathway (MDD-ICP) at the Centre for Addiction and Mental Health (CAMH), a structured, measurement-based care program. Over a two-year period, participants will undergo comprehensive clinical assessments covering demographics, childhood trauma, mood, anxiety, depression, sleep, suicidality, and physical activity. Actigraphy (GENEactiv) is used to objectively assess physical activity, sleep, and circadian rhythms over a 4-week period. Clinical data from electronic health records will be integrated into the analysis.

Results: To date 25 participants have been enrolled (mean age = 44.6 years, 87.5% females). Preliminary analysis of actigraphy-derived metrics demonstrates that participants exhibit on average 8.64 hours of sleep per night, 86% sleep efficiency (measure of immobility in x-y axis), and 19 milli-gravity units (measure of accelerometry) of physical activity. Preliminary analyses show positive non-significant correlations between MADRS scores with comorbid Agoraphobia ($r = 0.4223$) and PTSD ($r=0.3289$). Clustering analysis identified two potential subgroups: MDD with suicidality and MDD with comorbid conditions.

Conclusions: This study aims to improve the understanding of MDD heterogeneity to improve our understanding and inform the development of more individualized care strategies. Our preliminary results indicate that increasing sample size will be important for integrative analysis of clinical data and actigraphy metrics to potentially identify significant subgroups.

H.6: Accelerated deep transcranial magnetic stimulation for smoking cessation: A pilot open-label clinical trial

Student: Vincent Xi-Yu Wang, Supervisor: Bernard Le Foll

Background: Tobacco use disorder remains a leading cause of preventable mortality, with high relapse rates despite first-line pharmacotherapies. In 2020, deep transcranial magnetic stimualtion (TMS) targeting the insula received FDA approval for smoking cessation. Accelerated TMS (aTMS), an intensified protocol, has demonstrated superior efficacy in neuropsychiatric conditions like depression but has yet to be systematically evaluated for smoking cessation.

Objective: This study aims to evaluate the efficacy of an accelerated deep TMS protocol in achieving smoking abstinence.

Methods: This one-arm, open-label clinical trial will enroll 40 participants diagnosed with tobacco use disorder, targeting 30 completers. Participants will receive deep TMS using the H4-coil over five consecutive days (4 sessions/day, totaling 20 sessions). The primary outcome, point prevalence abstinence over the past seven days, will be verified using urine cotinine at Week 9 and self-reported smoking behavior using Timeline Followback. Secondary outcomes include craving reduction, withdrawal symptoms, and prolonged abstinence prevalence at Week 13. Participants will also be assessed for aTMS feasibility and acceptability.

Recruitment: Participants will be recruited from two hospitals in Ontario, including Waypoint Centre for Mental Health Care and Sunnybrook Health Sciences Centre. Clinical Trials Ontario will be used as an integrated platform to streamline regulatory processes and eliminate the need for multiple ethics applications across different recruitment sites.

Expected Impact: By consolidating treatment into one week, aTMS may enhance adherence and provide a rapid, effective intervention for smoking cessation. Findings will inform future comparative trials between accelerated and standard protocols.

Funding: This trial is expected to be supported by the PSI Foundation.

H.7: Discovering genetic biomarkers of neuronal vulnerability using post-mortem datasets from large brain banks

Student: Xiaolin Zhou, Supervisors: Shreejoy Tripathy

Background: Neuropsychiatric disorders are linked to brain composition changes, including cortical neuron loss in late-onset Alzheimer's disease (AD). Studies have highlighted the involvement of certain GABAergic cell types in dysregulating neural interactions and characteristics, contributing to the pronounced neurodegeneration. However, the relative inaccessibility of obtaining brain biopsies from human subjects hampers our understanding of how cell type proportions change in the brains of those with neuropsychiatric disorders.

Purpose and Hypothesis: This project aims to identify genetic factors governing cell-type vulnerabilities and their links to neuropsychiatric traits. We hypothesize that the selective vulnerability of different neuronal subtypes is associated with distinct genetic risk factors.

Methods: We benchmarked various cell-type deconvolution algorithms for bulk RNAseq data. Cell type proportion (CTP) estimates were validated against single-nucleus RNA sequencing (snRNA-seq) data from the same subjects. Subsequently, we performed the genome-wide association study (GWAS) and meta-analysis to discover genetic variants linked to variability in CTPs.

Results: Our findings demonstrate that MarkerGeneProfile (MGP) method achieves relatively high accuracy in estimating brain cell type proportions from bulk RNA-seq data. Furthermore, we found that employing approaches for accounting for technical covariates in RNAseq data significantly improved the power of GWAS analysis. And meta-analysis across cohorts of GWAS results leads to the robust identification of genetic variants associated with inter-subject variability in cell type proportions.

Conclusion: This study establishes that brain cell type proportions can be reliably inferred from bulk brain tissue RNAseq datasets. Moreover, we find that these proportions are in part governed by genetics.

H.8: Childhood trauma and PTSD linked with synaptic deficits: A PET study of [^{18}F]SynVesT-1 in youth seeking mental health treatment

Student: Maia Zilberman, Supervisors: Isabelle Boileau

Background: Adolescence is a key period for neurodevelopment, which can be negatively affected by trauma and stress. Preclinical literature links early life adversity to disturbances in synaptic proteins, potentially impacting mental health.

Purpose and Hypothesis: This study investigates the relationship between PTSD, childhood trauma and synaptic density in youth seeking mental health care, using PET imaging with [^{18}F]SynVesT-1. We hypothesize lower synaptic density in youth with PTSD.

Methods: Participants completed a PET scan with [^{18}F]SynVesT-1, a probe for synaptic vesicle glycoprotein 2A, a marker of presynaptic density. MRI was used to delineate six regions of interest: prefrontal, anterior cingulate, and temporal cortices, amygdala, hippocampus, and striatum. Time-activity curves were fitted using a simplified reference tissue model with the centrum semiovale as the reference region. Non-displaceable binding potential (BP_{nd}), an index of synaptic density, was estimated for each region and compared between groups.

Results: Twenty-five clinically diverse participants with (7M, 18F) and 25 without (10M, 15F) PTSD were included. PTSD participants were marginally older and had a higher rate of cannabis use disorder (CUD). ANCOVA controlling for CUD and age revealed that synaptic density was significantly lower in the temporal cortex (-12%, p=0.006) and marginally lower in the prefrontal cortex (-8%, p=0.08) in PTSD. These reductions correlated with emotional neglect scores on the Childhood Trauma Questionnaire (prefrontal cortex: p=0.014; temporal: p=0.05). A significant whole-brain main effect of emotional neglect (severe: n=14/44 vs non-neglected group: n=12/44) on synaptic density was observed ($F(1, 24)=5.7$, p=0.025).

Conclusion: The findings provide initial insights into how early life adversity may be associated with synaptic changes in this population, highlighting the importance of understanding these relationships in the context of mental health interventions.

I: Neuroscience & Brain Health

I.1: Building the human *in vitro* phenotype of *USH2A*-associated retinitis pigmentosa (RP): Early defects and late-stage photoreceptor degeneration in human stem cell-derived retinal organoids.

Student: Kristen Ashworth, Supervisor: Brian Ballios

Background/Purpose: Mutations in the *USH2A* gene are the leading cause of autosomal recessive retinitis pigmentosa (RP), an incurable blinding eye disease. The objective of this project was to establish the early and late structural and molecular human *USH2A* phenotype with the use of a novel, *USH2A*-mutated, patient-derived 3D-retinal organoid (RO) model.

Hypothesis: We hypothesize that *USH2A*-ROs will manifest phenotypic differences upon onset of *USH2A* expression; and, at mature stages, have a pathogenic structural and molecular outer retinal phenotype compared to healthy ROs.

Methods: ROs were derived from *USH2A*-mutated, patient induced pluripotent stem cells (PSCs) and two healthy human PSC control lines. ROs were assessed at early (Wk6), mid (Wk16–20), and late (Wk30–42) stages. Changes in cellular organization and morphology (retinal cell-specific protein expression, photoreceptor outer segment (OS) formation) were evaluated throughout RO development by immunohistochemistry and electron microscopy (EM). RT-qPCR was used to analyze gene expression.

Results: *USH2A* expression begins between Wk16–20 of RO development; at this time, phenotypic differences between healthy and *USH2A*-ROs emerge. At Wk16, expression of pan-photoreceptor precursor marker RCVN is decreased in *USH2A*-ROs compared to healthy ROs. By Wk20, cell death gene *Casp-3* is significantly upregulated in *USH2A*-ROs (p=0.017) and, structurally, outer nuclear layer thickness is significantly decreased (p=0.002) compared to healthy ROs. Between Wk30–42, *USH2A*-ROs show a distinct photoreceptor phenotype, including delayed brush border growth, limited photoreceptor OS formation (by transmission EM), and decreased photoreceptor cell surface density (by scanning EM) compared to healthy ROs. At Wk42, *USH2A*-ROs have significantly shorter brush border length (p=0.004) and decreased expression of mature photoreceptor markers Arr3 (p=0.036) and CRX (p=0.035) compared to healthy ROs.

Conclusion: *USH2A*-ROs show early reductions in retinal-specific protein and gene expression from Wk16–20, followed by pronounced abnormalities in photoreceptor growth, maturation, and OS formation at Wk30–42. These findings provide novel insights into the temporal progression of *USH2A*-RP and may help inform future therapies for this currently-incurable blinding eye disease.

I.2: Investigating the CXCR4/CXCL12 axis to predict multiple sclerosis symptom onset

Student: Gabriela Blaszczyk, Supervisor: Raphael Schnieder, Tom Schweizer

Background: Multiple Sclerosis (MS) is a neuroinflammatory disease characterized by immune cell infiltration and lesions in the central nervous system (CNS). Radiologically Isolated Syndrome (RIS) is a term used when lesions which fulfil strict radiological criteria for MS are present in the CNS without the associated symptoms and is believed to be the precursor to MS with variable outcome. Clear, accessible, and reproducible approaches to estimate prognosis for persons with RIS (pwRIS) remain to be developed. In an immune-driven disease such as MS, early changes in peripheral blood may allow for prediction of disease progression while contributing additional insight into early CNS trafficking of immune cells.

Purpose: We propose to study peripheral blood mononuclear cell and spinal fluid (CSF) samples of pwRIS, pwMS and healthy control (HC) individuals to determine a pattern and improve in-clinic treatment for pwRIS. Selected for this study is the lymphocyte migration receptor CXCR4, that has been implicated to be an MS-specific biomarker, and its ligand CXCL12.

Hypothesis: If CXCL12 and CXCR4 are being upregulated, then this axis may be contributing to early MS disease pathogenesis and neuroinflammation.

Methods: Following collection of peripheral blood, the samples were phenotyped ex-vivo by Cytometry by Time of Flight, particularly focusing on T cell migration and activation markers. Following collection of CSF, an Ella assay was performed to titer levels of CXCL12 and correlated to markers of neurodegeneration from the same donors.

Results: Significant upregulation of CXCR4 was observed on multiple lymphocyte subsets in pwRIS, including MS-relevant subsets. CXCL12 levels in pwRIS and pwMS CSF were observed to have increased significantly in comparison to HC. These levels positively correlated to both GFAP and NfL levels in CSF.

Conclusions: We have shown that CXCR4 is upregulated on several lymphocyte subsets, suggesting an aberrant immune response leading to early CNS trafficking. CXCL12, a proposed ligand for early CNS chemotaxis and entry, is upregulated in the CSF of pwRIS and pwMS. We found that CXCL12 levels correlate with established markers of CNS damage (NfL, GFAP), suggesting a potential use for early prognosis. These findings will be central in the improvement in clinical care of pwRIS by providing a tool to estimate prognosis and allow for specialized treatment, while understanding the pathophysiology of early disease.

I.3: Sox10-mediated direct lineage reprogramming of inflammatory astrocytes into oligodendrocytes

Student: Rachel Gibbs, Supervisor: Maryam Faiz

Background: Direct lineage reprogramming (DLR) is a new strategy for brain repair. With the goal of replacing oligodendrocyte lineage cells (OLCs) lost in disease, we previously demonstrated DLR of McCarthy-de Vellis (MD) serum-cultured astrocytes into induced OLCs (iOLCs) using the transcription factor, *Sox10*.

Purpose and Hypothesis: Although this approach showed promise, astrocytes exhibit significant heterogeneity, and disease-specific astrocyte states may influence DLR outcomes. To address this knowledge gap, we investigated iOLC DLR in a well-characterized neurotoxic astrocyte state implicated in various neurological diseases.

Methods: We used two *in vitro* models: MD serum astrocytes cultured from P4-P6 Aldh1l1-creERT2;Ai14 mice and immunopanned (IP) serum-free astrocytes from P3-P7 Ai14 mice. Cells were stimulated with TNFα, IL1α, and C1q (TIC) to induce a neurotoxic astrocyte phenotype for 24 hours before transduction with LV-GFAP::Sox10 or an LV-GFAP control.

Results: Following transduction of TIC-responsive MD astrocytes with LV-GFAP::Sox10-ZsGreen, we found a higher percentage of ZSGreen+ OLCs stained for PDGF at D6, O4 at D10, and MBP at D14 compared to non TIC-treated and zsGreen only controls. TIC-treated IP astrocytes also showed a higher percentage of iOLCs in LV-GFAP::*Sox10*-Cre transduced cells at D12 compared to LV-GFAP::Cre transduced controls. Further, through stringent lineage tracing, we demonstrated that reprogrammed OLCs originate from ALDH1L1+ astrocytes.

Conclusions: Together, these findings demonstrate that inflammatory astrocytes are amenable to DLR. This approach could be valuable for targeting disease-specific astrocyte populations while simultaneously replacing lost OLCs.

I.4: Decoding spatiotemporal transcriptome remodeling in spinal cord injury

Student: Akshat Modi, Supervisor: Michael Fehlings

Background: Spinal cord injury (SCI) triggers dynamic transcriptomic remodeling across spatially distinct compartments rostral and caudal to the lesion core. Understanding these region-specific and region-shared transcriptional changes across subacute and chronic phases of SCI is crucial for identifying molecular drivers of repair and regeneration.

Purpose: This study aims to characterize the spatiotemporal transcriptomic landscape of SCI using spatial transcriptome datasets. By mapping gene expression changes across multiple compartments, we seek to uncover unique patterns of cellular and molecular responses contributing to SCI progression.

Hypothesis: We hypothesize that transcriptomic remodeling exhibits unique spatial patterning across regions rostral and caudal to the lesion core. Additionally, we propose that transient transcriptome remodeling may occur in the subacute phase which either converges toward the uninjured state or diverges toward a persistently altered state in a compartment-specific manner during the chronic phase.

Methods: We processed and interrogated a spatial transcriptomics dataset of mice following moderate thoracic spinal cord injury at the subacute phase (7 days) and the chronic phase (2 months) post-injury, compared to uninjured controls. We analyzed differentially expressed genes across several spatial compartments spanning rostral and caudal regions relative to the lesion core. Unsupervised clustering was performed to identify transcriptomic similarities and differences between compartments. Principal component analysis was performed to assess region-specific transcriptomic shifts in subacute and chronic SCI. Functional enrichment analysis was conducted to determine region-specific versus region-shared biological processes and pathways. Cell deconvolution was applied to infer the cellular composition of each compartment.

Results: Unsupervised clustering and principal component analyses revealed striking transcriptomic symmetry in acute and subacute SCI phases, where compartments rostral and caudal to the lesion core at similar distances exhibited highly similar gene expression patterning. We also determined that this unique patterning remains conserved at the functional level with shared key secondary injury cascade events. Ongoing cell deconvolution and principal component analyses will further elucidate the cellular drivers and trajectory of subacute and chronic SCI remodeling.

Conclusion: Our findings suggest that transcriptomic remodeling after SCI follows a symmetric spatial pattern, with distinct regional signatures influencing repair and regeneration. By identifying compartment-specific and symmetric molecular programs, this study provides insights into both potential therapeutic targets and spatially relevant intervention sites for SCI treatment.

I.5: Investigating the synaptic integration of neural progenitor cell progeny into lesioned forelimb motor circuitry following cervical spinal cord injury

Student: Karan Patel, Supervisors: Michael Fralick

Background: Cervical spinal cord injuries (SCI) result in debilitating permanent neurological deficits including the loss of upper and lower limb motor function. The transplantation of human induced pluripotent stem cell-derived neural progenitor cells (hiPSC-NPCs) into the spinal parenchyma has emerged as a promising pre-clinical regenerative strategy to restore voluntary motor control. NPC-derived neurons are believed to bridge lesioned brain-derived projections including the corticospinal tract, rubrospinal tract, and reticulospinal tract, and spared neuronal populations below the injury. However, it is currently unclear which descending circuit(s) are crucial for recovery of forelimb function and how they can be recruited to enhance recovery.

Purpose: Transduction of neuronal impulses from the brain to the forelimb muscles following SCI requires a graft-derived neuron to bridge the lesioned descending inputs and spared neurons below the injury. Interrogating the synaptic integration of NPCs into each motor pathway may reveal mechanistic insights that can be leveraged to enhance the integration of cells into particular circuits.

Hypothesis: NPC-derived neurons synaptically bridge the descending motor circuits innervating forelimb muscles to promote the recovery of upper limb motor function.

Methods: Female adult immunodeficient Rowett Nude (RNU) rats received a clip compression-contusion SCI at level C6/C7 of the spinal cord to model traumatic SCI in humans. Animals received a cell transplantation two weeks post injury into the spinal parenchyma and will receive stereotaxic intracranial injections of adeno-associated viruses (AAVs) at 14 weeks post-transplant. Tissue will be harvested at 20 weeks post transplantation and histological assessments will be performed to visualize synaptically integrated cells.

Results: Corticospinal, rubrospinal, and reticulospinal projections to the forelimb motor columns were traced using AAVs in uninjured rats for proof of concept. Transgenic NPCs were prepared by piggyBac mediated mutagenesis in the iPSC state, followed by subsequent neural induction to form transgenic NPCs that will restrict the expression of a fluorescent reporter to circuit-integrated graft-derived neurons.

Conclusions: NPC-derived neurons synaptically integrated with presynaptic brain-derived projections can be visualized to highlight the recruitment of each bridged circuit on forelimb functional recovery.

I.6: Condition-specific astrocyte heterogeneity, crosstalk, and transcriptional network diversification after spinal cord injury

Student: Zeenal Patel, Supervisor: Michael Fehlings

Background: Spinal cord injury (SCI) initiates a multifaceted glial response that governs devastating clinical manifestations, including paralysis, hypoesthesia, and dysautonomia. Astrocytes play a pivotal role in post-SCI repair by modulating inflammation, maintaining tissue integrity, and supporting neuronal survival. However, their transcriptional and functional responses are highly dynamic, varying across time, injury severity, biological sex, age, and injury type. Elucidating these condition-specific astroglial adaptations is imperative for the development of targeted therapeutic interventions aimed at optimizing recovery.

Purpose and Hypothesis: This study seeks to systematically characterize astrocyte-specific gene expression profiles and intercellular communication dynamics to delineate how astrocyte heterogeneity influences injury progression and repair mechanisms. We hypothesize that astrocytes exhibit context-dependent transcriptional heterogeneity following SCI, driven by distinct molecular programs that evolve across injury parameters.

Methods: We examined astrocyte diversity post-SCI using single-nucleus RNA sequencing datasets on spinal cord astrocytes from various experimental conditions: different time points post-injury, injury severities, sex, age groups, and injury models. Differential gene expression analysis identified key transcriptional shifts underlying astrocytic response. Hierarchical clustering and functional enrichment categorized astrocyte subtypes by molecular signatures and biological pathways. We modelled ligand-receptor interactions to explore astrocyte communication with neurons, microglia, oligodendrocytes, ependymal cells and vascular cells. All statistical analyses were validated through permutation-based enrichment testing.

Results: Our analyses uncovered substantial transcriptional heterogeneity among astrocytes post-SCI, revealing distinct injury-contextualized gene expression patterns. Differential expression analysis identified dynamic shifts in astrocytic subpopulations, where early-phase reactive astrocytes exhibited upregulation of pro-inflammatory mediators, while chronic-phase astrocytes transitioned toward reparative transcriptional states. Injury severity dictated astroglial responses, with severe injuries sustaining prolonged inflammatory signalling, whereas milder injuries favoured neuroprotective pathways. Sex-specific analyses showed that females highly expressed neuroprotective genes, while males exhibited higher levels of metabolism, protein turnover, and cellular stress response genes, suggesting more active cellular maintenance. Age-related disparities highlighted a pronounced regenerative and proliferative potential in young adult astrocytes, while aged astrocytes displayed impaired metabolic resilience and diminished reparative capacity. Ligand-receptor interaction analysis mapped condition-dependent astrocyte-neuron and astrocyte-microglia communication networks, implicating key molecular pathways in secondary injury progression. Functional enrichment pinpointed critical astrocyte-associated pathways, including apoptosis, metabolic homeostasis, and cell-signalling cascades.

Conclusion: Collectively, these findings delineate a comprehensive, condition-specific astroglial transcriptional framework, providing novel insights into molecular targets for SCI therapeutics. Furthermore, this study establishes a statistically validated, high-resolution transcriptional atlas of astrocyte responses to SCI, revealing injury-contextualized astroglial subpopulations and signalling networks. By integrating differential gene expression and ligand-receptor interaction analyses, we identify condition-specific molecular targets that may be leveraged to modulate astrocyte-mediated neuroprotection and enhance functional recovery post-SCI.

I.7: The effect of roflumilast on regeneration and functional recovery in a rat model of cervical spinal cord injury

Student: Mehraein Roointan, Supervisor: Charles Tator

Background: Spinal cord injury (SCI) is a life-altering condition with limited recovery prospects. Cervical SCIs (CSCIs) result in severe impairments and death. Secondary injury events, including neuroinflammation, cell death, and glial scar formation, inhibit repair and regeneration. Stimulating endogenous ependymal neural stem/progenitor cells (epNSPCs) in the spinal cord to differentiate into neurons is a promising therapeutic strategy. Cyclic adenosine monophosphate (cAMP) regulates inflammation and repair processes. Post-SCI, phosphodiesterase-4 (PDE4) enzymes hydrolyze cAMP, impeding recovery. Roflumilast, an FDA-approved PDE4 inhibitor, prevents cAMP degradation. In models of brain injury and thoracic SCI, Roflumilast has shown anti-inflammatory effects and improved outcomes. However, its efficacy in CSCI models and its effect on epNSPCs remain unexplored.

Purpose: We aim to fill this gap by performing in vivo and in vitro experiments to assess the effect of Roflumilast on epNSPCS, as well as using a clinically relevant model of CSCI to assess its effect on functional recovery.

Hypothesis: We hypothesize that in our CSCI model, Roflumilast will enhance epNSPC proliferation, stimulating repair and regeneration, leading to functional recovery.

Materials and Methods: To test Roflumilast's effect on epNSPCs, we performed in vitro and in vivo experiments. In vitro, epNSPC cell lines were treated with Roflumilast. In vivo, female Wistar rats underwent acute clip compression injury at the C6-C7 level, and 1 hour after injury were randomly assigned to receive i.p. injections of the vehicle or Roflumilast (1 mg/kg) followed by daily injections until 10 days post-SCI. Functional recovery was assessed with multiple behavioral assays for 6 weeks post-SCI.

Results: Both in-vitro and in-vivo experiments showed increased epNSPC proliferation with Roflumilast. By 1-week post-SCI, the Roflumilast group had a significantly higher BBB score of 8, indicating plantar paw placement with no weight support, compared to the control group's score of 5, indicating slight hindlimb movement. This improvement highlights Roflumilast's potential in enhancing functional recovery.

Conclusion: Our findings support the hypothesis that Roflumilast enhances epNSPC proliferation, promoting repair and regeneration. This study suggests that Roflumilast, an FDA-approved drug, could be repurposed for SCI treatment to improve functional recovery and expedite clinical trials.

I.8: *Crb1*-mutation increases differentiation into early-born retinal cell types in human induced pluripotent stem cell-derived retinal organoids

Student: Jessica Wang, Supervisor: Brian Ballios

Background: *CRB1* mutations account for ~10% of all genotypes associated with two common inherited retinal diseases, causing incurable vision loss in children and young adults. However, the mechanisms of *CRB1*-associated disease are difficult to study due to a lack of models that accurately replicate human disease, and the pathogenesis is unclear. As such, to recapitulate human disease development, human retina organoids (ROs) show great promise as an *in vitro* model.

Purpose: This study aims to 1) characterize an *in vitro* phenotype and 2) identify potential molecular disease mechanisms of *CRB1*-associated disease.

Hypothesis: This study hypothesizes that *CRB1*-mutated ROs would have increased differentiation into early-born retinal cell types at the expense of late-born cell types.

Methods: ROs were generated from two iPSC lines: a healthy donor line (hRO) and a *CRB1*-disease patient line (cRO). Immunofluorescent staining for cell-type specific markers was performed. Proliferation was measured by incubating the ROs in EdU for 1 hour and either fixing immediately (single pulse) or fixing after a 24 hour incubation in EdU-free media (pulse-chase). RNA was extracted from whole ROs to quantify gene expression using qRT-PCR.

Results: The percentage of early-born BRN3a+ ganglion cells in the ganglion cell layer at week 8 (cRO: 74%, hRO: 18%, $p< 0.01$) and ARR3+ cones in the outer nuclear layer at week 16 (cRO: 46%, hRO: 11%, $p<0.04$) were significantly higher in cROs compared to hROs. However, the percentage of later-born OTX2+ bipolar cells in the inner nuclear layer was significantly lower in cROs at weeks 20 (cRO: 6%, hRO: 33%, $p<0.02$) and 28 (cRO: 2%, hRO: 34%, $p<0.01$). Relative to hROs following a pulse-chase, cROs had a higher percentage of the total EdU+ cells located in the basally (cRO: 19%, hRO: 14%, $p<0.02$). The expression of *NOTCH* effector *HEY1* was significantly decreased in CROs compared to age-matched controls (hRO: 1) at week 8 (cRO: 0.7, $p<0.05$) and week 40 (cRO: 0.8, $p<0.03$).

Conclusions: The cell population shift suggests depletion of the progenitor pool by early-born cells, resulting in a decreased number of late-born cells vital to retinal function. The basal localization of proliferating cells implies a defect in interkinetic nuclear migration, which may underlie the laminar disorganization observed clinically. These results indicate that prior to degeneration, *CRB1*-associated disease may cause developmental anomalies potentially mediated by the *NOTCH* pathway.

J: Infection & Immunology

J.1: In-depth T-cell phenotyping and its association with relapse in transplant recipients with human cytomegalovirus (HCMV) DNAemia

Student: Golnaz Amidpour, Supervisors: Atul Humar

Background: It is estimated that 20-30% of solid organ transplant (SOT) recipients with human cytomegalovirus (HCMV) DNAemia will develop relapse despite antiviral treatment. HCMV relapse can lead to HCMV disease, increased allograft rejection risk, antiviral toxicity and resistance, higher morbidity, and mortality.

Purpose and Hypothesis: We aimed to perform an in-depth analysis of T-cell subsets associated with clinical HCMV relapse, assessing exhaustion, activation, and effector markers in $CD4^+$ and $CD8^+$ T cells. We hypothesized that higher activation and effector levels, with lower exhaustion markers, enhance long-term protection against relapse.

Methods: Blood was collected in 33 SOT recipients at the onset of HCMV DNAemia and 4 weeks later. A unique 25-colour multiparameter flow cytometry panel was used to identify key subsets among global and HCMV-specific T-cells. Relapse was defined as plasma viral load >1,000 IU/mL after initial clearance, within six months of the initial episode.

Results: The median age of participants in the study was 59.0 years [min-max: 23.0-76.0 years]. The median time from transplant to onset of DNAemia was 255 days [min-max: 22-7591 days]. Thirteen participants (39.4%) developed relapse within six months of the initial episode. HCMV antigen-specific T-cell responses were overall low in our cohort and did not vary between those with and without relapse. However, several global T-cell subsets were significantly lower in SOT recipients that developed relapse, including granzyme B^+ $CD4^+$ T cells (p=0.009 at onset of DNAemia, p=0.047 at 4 weeks) and $CD154^+$ $CD4^+$ T-cells (p=0.003 at 4 weeks), and lower frequencies of granzyme B^+ (p=0.038) $CD8^+$ T-cells at the onset of DNAemia. Multi-marker exhaustion analysis of global T-cell subsets revealed that several were significantly lower in SOT recipients who developed relapse, including $CD16o^-$ $CTLA\text{-}4^-$ $LAG\text{-}3^+$ $PD\text{-}1^+$ $TIGIT^+$ $TIM\text{-}3^-$ $CD4^+$ T-cells (p=0.025 at DNAemia) and CD8+ T-cells (p=0.004 at DNAemia), and higher frequencies of $CD16o^-$ $CTLA\text{-}4^+$ $LAG\text{-}3^-$ $PD\text{-}1^-$ $TIGIT^+$ $TIM\text{-}3^-$ $CD8^+$ T-cells were observed (p=0.044 at 4 weeks). These results suggest that granzyme B , CD154 and CD16o CTLA-4 LAG-3 PD-1 TIGIT TIM-3 expression on global T-cells may serve as biomarkers predicting relapse risk and that processes like cytotoxicity and exhaustion may play important roles in the pathogenesis of HCMV relapse in transplant recipients.

J.2: Profiling HBsAg-specific B cells in hepatitis B functional cure patients

Student: Agustina Crespi, Supervisor: Adam Gehring

Background: Chronic Hepatitis B virus (HBV) infection leads to liver inflammation, which can result in fibrosis, cirrhosis, and cancer. Clinical trials for new HBV therapies aim to achieve functional cure, defined as sustained undetectable HBV DNA and loss of HBV surface antigen (HBsAg) off treatment. Recent clinical trials suggest that anti-HBs may serve as a marker for the durability of functional cure. This observation, coupled with data showing that 80% of chronic hepatitis B (CHB) patients treated with B cell-depleting therapies experience HBV reactivation, highlight the importance of B cells in controlling chronic HBV infection.

Persistent antigen exposure leads to dysregulation of adaptive immunity. Recent studies demonstrate that HBsAg-specific B cells from CHB patients failed to produce antibodies, were enriched with an atypical memory B cell phenotype, and expressed the inhibitory marker PD-1. Whether the phenotypic and functional profile of B cells is restored with loss of HBsAg in functional cure patients has not been studied and may represent a critical pathway to HBV control in clinical trials.

Purpose: This research explores how loss of persistent antigen exposure impacts B cell phenotype and function. Evaluating how HBsAg loss correlates with changes in B cell characteristics and functional capacity could provide a better understanding of their role in viral control. These insights could improve immunotherapies targeting T & B cell immunity and increase functional cure rates by targeting specific B cell functions.

Hypothesis: It is hypothesized that HBsAg loss reorganizes the phenotypic distribution of HBsAg-specific B cells and enhances their functional capacity to produce antibodies and cytokines.

Methods: HBsAg-specific B cells will be identified using fluorescently tagged HBsAg baits and a flow cytometry panel to phenotype B cell subtypes. Sorted HBsAg-specific B cells will be expanded and differentiated in culture into antibody-producing cells to assess their functional capacity. Samples from healthy vaccinated controls, CHB patients, and CHB functional cure patients will be analyzed.

Results: Thus far, flow cytometry staining and fluorescently tagged HBsAg bait usage has been optimized. Optimization experiments determined a sequential staining method with cells stained with baits alone for 45 minutes, followed by staining with surface marker antibodies for 30 minutes. This method was determined to minimize non-specific binding on naïve B and T cells while maximizing binding on memory B cells.

Conclusion: The antigen bait method has been optimized in healthy controls. Next steps include staining HBsAg+ and HBsAg loss patient samples. Flow cytometry will characterize B cell phenotypes, and HBsAg-specific B cells and their production of anti-HBs will be assessed.

J.3: Investigating the role of complement in proteinuric chronic kidney disease progression

Student: Vienna Fu, Supervisor: Christoph Licht

Background: Each time the heart pumps, ~20% of the cardiac output flows through the kidneys where it is filtered by millions of nephrons. Blood first enters the glomerular compartment of the nephron where it is filtered by a permselective barrier which prevents the passage of various molecules including plasma proteins. Filtered fluid then passes through the tubular compartment of the nephron where molecules can be secreted and/or reabsorbed. The remaining filtrate is then excreted from the body. Various conditions can result in a weakened filtration barrier, allowing plasma proteins to leak into the tubular space – a process called proteinuria. These escaped proteins damage the glomerulus and more notably, the renal tubules, leading to tubulointerstitial (TI) fibrosis and renal function decline – hallmarks of chronic kidney disease (CKD). Therefore, proteinuria plays a key role in CKD progression, however the specific mechanisms involved remain unknown. Evidence suggests that circulating complement proteins involved in innate immunity leak into the tubular space during proteinuria. Evidence also suggests that tubular cells synthesize complement proteins in response to protein aggravation, thus exacerbating potential tubular complement activity. However, the specific effects of these ultrafiltered and locally synthesized complement proteins on kidney damage are yet to be explored.

Purpose and Hypothesis: Our study aims to explore the role of complement in proteinuric CKD progression. We hypothesize that complement plays a key role in TI inflammation and fibrosis, thus contributing to proteinuric CKD progression.

Methods: RNA sequencing was completed on kidney biopsies from patients with proteinuric CKD and healthy controls. The differential expression of complement genes between patients and controls were then determined. In vitro studies were then conducted to confirm and further explore human RNA sequencing results. Tubular epithelial cells were treated with various plasma proteins prior to quantifying complement expression and inflammatory signaling.

Results: Overall, complement genes were upregulated in patient kidneys compared to controls. Greater upregulation was observed in tubular compartments compared to glomeruli, suggesting a greater role of complement in tubular pathology. This robust complement upregulation observed in the renal tubules of patients, along with its respective pro-inflammatory effects were confirmed following in vitro treatment of tubular cells with the plasma protein transferrin.

Conclusion: During proteinuria, escaped plasma proteins, particularly transferrin, induce robust complement synthesis in the TI, suggesting a role of complement in tubular pathology. Therefore, complement plays a key role in proteinuric CKD progression and its inhibition may have therapeutic potential.

J.4: Epidemiological update on febrile returned travelers to Ontario from the Rapid Assessment of Febrile Travelers (RAFT) program

Student: Gregory Hawley, Supervisor: Andrea Boggild

Background: Fever is a common presenting complaint that occurs in 17% of all returned international travelers. Although fever is frequently attributable to self-limited infections such as traveler's diarrhea or cosmopolitan viral respiratory illnesses, it may also be the initial or sole manifestation of potentially life-threatening illnesses or infectious processes with public health implications. National guidelines were developed to standardize clinical practice and improve outcomes, resulting in the implementation of a site-specific Rapid Assessment of the Febrile Traveler (RAFT) program.

Purpose and Hypothesis: In addition to standardizing patient care, the RAFT program facilitates collection of epidemiological data regarding fever in the returned traveler. The RAFT program was initially evaluated between February 2014 and December 2015, the first 22 months of the RAFT clinic implementation. The epidemiology of febrile travelers has not been updated since this time, despite the continued expansion of international travel and referral to the RAFT program. Our hypothesis is that the majority of patients continue to be diagnosed with syndromic or clinical-level diagnoses that are not delineated to a pathogen-level despite use of reference-level microbiologic investigations.

Methods: All febrile returned travelers between 2016-2018 were assessed for eligibility. For all patients, demographics, complete travel history, and final diagnoses were collected. Travel history was reviewed to assign a geographic region of travel. Final diagnoses were collected at the microbiologic level, where available. In cases where no microbiologic etiology was determined, a clinical or syndromic diagnosis was made. The data collected was then analyzed using descriptive statistics.

Results: 464 patients presenting via the RAFT program between 2016-2018 were included in the study. The most common regions of geographic travel were Southeast Asia (n=111, 23.92%), Caribbean (n=99, 21%), and East Africa (n=65, 14%). The most commonly represented clinical syndromes were non-specific viral syndrome (n=122, 26%), gastrointestinal syndrome (n=121, 26%), respiratory syndrome (n=101, 22%), and vector-borne illness (n=62, 13%). The most common diagnoses were viral syndrome (n=110, 24%), traveler's diarrhea (n=45, 10%), viral upper respiratory tract infection (URTI) (n=39, 8%), flavivirus infection (n=36, 8%), and influenza (n=29, 6%). Potentially life-threatening travel-related illnesses were well represented in the patient population, including Dengue fever (n=27, 6%), enteric fever (n=17, 4%), and malaria (n=10, 2%). When considering additional pathogens of potential public health importance, there were four cases of tuberculosis (1%), one case of mumps (0.2%), and one case of varicella (0.2%).

Conclusions: This study serves as an epidemiological update of our rapid assessment of febrile travelers program. Despite serious travel-related infections such as enteric fever, Dengue fever, and malaria being well represented in our population, the three most common diagnoses were non-specific viral syndrome, traveler's diarrhea, and viral upper respiratory tract infection, all of which had an absence of microbiologically confirmed pathogen. The lack of microbiologic diagnosis reflects an important diagnostic gap in our patient population, with potential implications for patients, health care providers, and public health systems. The need for novel, high throughput platforms for microbiologic testing is evident in order to improve epidemiological surveillance and diagnostic closure in febrile returned travelers.

J.5: Glycosylation abnormalities in nephrotic syndrome: Unraveling the underlying causes

Student: Artashes Keshishyan, Supervisor: Mathieu Lemarie

Background: Nephrotic syndrome (NS) is a poorly understood kidney disease characterized by the loss of protein in the urine due to glomerular pathology. Recent published data suggest that some NS patients' kidney biopsy (KBx) exhibit reduced glomerular sialylation. However, the lectins used (HPA and SNA) were not optimized to evaluate this lesion type, but instead suggested a more complex glycosylation defect.

Purpose and Hypothesis: In NS, reduced glomerular sialylation observed on KBx is due to a combined deficiency in terminal galactose and sialic acid rather than a pure sialic acid defect. The purpose of our study is to provide evidence that a subtype of NS is caused by the cleavage of both galactose and sialic acid by a pathogenic enzyme.

Methods: We stained patient KBx with the lectins MALII, HPA, PNA, ECL, and SNA. To investigate this phenomenon further, we measured sialic acid in patient urine samples using a fluorometric assay. To demonstrate that sialic acid is detectable upon an extracellular enzymatic cleavage, we injected *S. pneumoniae* SpNanA in lab rats and measured urine sialic acid after an hour of injection. SpNanA is an enzyme that cleaves sialic acid. Rat kidney tissues were also stained with lectins after multiple timepoints post-injection to determine the time it takes for glycoproteins to get recycled on cells.

Results: None of the patient's kidney tissues stained with PNA, which would have been the case if solely sialic acid was absent. HPA signal showed that galactose is absent as well. Moreover, we successfully detected sialic acid in patient urine samples. Sialic acid was also detected in rat urine, demonstrating that sialic acid pools in the urine upon an extracellular cleavage. PNA lectin stains of rat kidney tissues showed that it took approximately 120 hours for glycoproteins to get recycled with sialylated glycan chains.

Conclusion: We hypothesized that if the problem were solely a synthetic defect, sialic acid will not be detected in significant levels in the urine. Through our lectin stains and urine sialic acid measurements, we demonstrated a broader understanding that provides evidence of an extracellular cleavage etiology to nephrotic syndrome rather than being a genetic defect. This is significant, as urine sialic acid testing can also become a powerful diagnostic tool for NS in the clinic.

J.6: MicroRNA-based therapies as potential treatment for SARS-CoV-2 induded acute respiratory distress syndrome

Student: Jacqueline Pavelick, Supervisor: Claudia Dos Santos

Background: Acute Respiratory Distress Syndrome (ARDS) is a leading cause of respiratory failure and mortality in severe COVID-19 cases, with no effective treatments available. A potential treatment option is microRNA (miRNAs) based therapies that regulate gene expression. Our patented miRNAs, NMoo1 and NMoo2, have shown potential to mitigate lung injury in previous preclinical Sepsis and Influenza models. NMoo1 displays anti-inflammatory properties by suppressing the production of Tumour Necrosis Factor alpha (TNFα) and Interleukin 6 (IL-6). NMoo2 exhibits pro-inflammatory characteristics by disrupting tight junctions, thereby facilitating virus entry into cells.

Purpose and Hypothesis: This study evaluates NMoo1 and NMoo2 as potential treatments for SARS-CoV-2 induced ARDS. We hypothesize that NMoo1 and NMoo2 play a role in disease progression of SARS-CoV-2 induced ARDS by modulating inflammatory and antiviral responses.

Methods: To investigate the progression of SARS-CoV-2 infection and inflammatory responses in the respiratory tract, we conducted a 10-day survival study using K18-hACE2 transgenic mice intranasally infected with SARS-CoV-2 strain VIDO. Mice were sacrificed on day 3 post-infection (3 mock-infected and 3 infected mice), while the remaining infected mice were sacrificed at humane endpoints on days 4 and 5. Lung tissues were analyzed via histopathology, quantitative real-time PCR (qRT-PCR), and digital droplet PCR for cytokines, antiviral genes, and miRNAs.

Results: We confirmed the presence of the SARS-CoV-2 virus in the lungs by detecting the Nucleocapsid, RNA-dependent RNA polymerase, and Open Reading Frame 1a genes via qRT-PCR. Histological analysis revealed increased inflammation, aligning with elevated expression levels of proinflammatory cytokines (TNFα and Interleukin-1β), and antiviral response genes (Interferon-γ and Interferon-β). NMoo1 exhibited no significant change while NMoo2 showed a significant downregulation in infected mice in comparison to mock controls, suggesting a potential role in SARS-CoV-2 pathogenesis.

J.7: Rehabilitating gastric aspiration lungs with a JAK/STAT inhibitor

Student: Matheus Saraiva de Morais, Supervisor: Marcelo Cypel, Lorenzo Del Sorbo

Background: Lung transplantation is the gold-standard treatment for end-stage lung disease. However, access to this life saving treatment is constrained by the shortage of suitable donor organs. In fact, donor lungs have the lowest transplantation acceptance rate among solid organs, at only 20%. Approximately 15% of the declined lungs are due to the aspiration of gastric contents, a common phenomenon among intubated patients, including donors.

Purpose and Hypothesis: The regeneration of gastric aspiration lungs during Ex-Vivo Lung Perfusion (EVLP) presents an opportunity to greatly expand the pool of donor lungs. This isolated platform allows for further lung functional assessment and for the targeted delivery of anti-inflammatory drugs at higher concentrations and lower side effects. This study hypothesizes that the addition of the JAK1/JAK2 inhibitor Ruxolitinib to the EVLP solution can recover the function of gastric aspiration lungs for transplantation.

Methods: Gastric aspiration injury will be induced in donor pigs by bronchoscopically delivering 110mL of gastric content into both lungs. Pigs will be ventilated for 2 hours following the injury to allow for injury establishment. Donor lungs will be harvested and stored at 10 C° for 12 hours to recreate a modern lung transplant scenario, and then perfused for 6 hours on EVLP. A total of 8 pigs (30-35 kg) will be used: 4 lungs will be perfused with standard EVLP solution (control), and 4 with Ruxolitinib added (treatment).

J.8: The pro-inflammatory score: A method for assessing disease activity in patients with juvenile idiopathic arthritis (JIA)

Student: Kevin Ymeri, Supervisor: Rae Yeung

Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatic disease in children. This disease is characterized by prolonged synovial inflammation with a range of symptoms, but most notably joint pain. Clinical tools like the Juvenile Arthritis Disease Activity Score (JADAS) are widely used to assess disease activity, but it does not capture underlying biological mechanisms that influence disease activity, which is known to miss subclinical disease activity. Potential pro-inflammatory genes have been identified through previous work in our lab using clustering and data-driven techniques of microarray data in patients with high disease activity. These may serve as potential biomarkers in the first steps towards develop a pro-inflammatory score. These genes or biomarkers associated with inflammation can form a pro-inflammatory score that accurately correlates with disease activity in JIA. This study aims to (1) identify gene signatures driving inflammation in JIA using machine learning and (2) develop a computational tool that integrates gene expression data with clinical disease activity measures. Patients from the UCAN-CAN-DU study, an international initiative focused on precision medicine in JIA, were stratified into high and low disease activity groups based on JADAS71 scores and cytokine expression. Feature selection was performed on patient-derived genes from NanoString data using differential gene expression analysis and further machine learning techniques. Selected genes were used to compute patient-specific arithmetic and geometric mean scores, which were compared using Pearson correlation and Wilcoxon rank-sum tests. XGBoost (AUC 0.86) performed better than LASSO regression (AUC 0.82) in feature selection and seven genes were obtained from the XGBoost model. The Pearson correlation-coefficient between scores was 0.84. Future work will extend this model across the full disease activity spectrum using multinomial logistic regression and validate findings in an independent cohort as well as exploring other feature selection techniques. This study serves as a proof of concept for integrating gene expression into clinical assessment. In addition, this approach will also be extended to RNA sequencing data, enabling the analysis of a broader range of genes as potential biomarkers for the pro-inflammatory score. Ultimately, this project aims to improve the detection of subclinical or biological disease activity in JIA, helping to determine potential treatment plans.

K: Regenerative Medicine & Development

K.2: Investigating the role of the cytoskeleton regulator RhoB in kidney tubular cells

Student: Olanike Akinola, Supervisor: Katalin Szaszi

Background: Kidney fibrosis is an urgent public health issue. It is the common final pathway of numerous progressive kidney diseases. It is characterized by increased extracellular matrix (ECM) protein production and deposition, destruction of functional tissues, inflammatory cell infiltration, and fibrotic transformation of resident cells, including the tubules. These changes diminish kidney function, ultimately leading to end-stage kidney. Kidney fibrosis is mostly caused by diabetes and hypertension. Currently, there is no cure. The treatment options, which are dialysis and transplant, reduce the quality of life of patients and place a huge financial burden on the economy. However, the molecular pathology underlying kidney fibrosis remains poorly understood; thus, new insights are urgently needed to identify effective therapeutic targets for kidney fibrosis.

Kidney tubules have emerged as important initiators of fibrosis, as they start secreting pathogenic pro-fibrotic mediators upon injury. Rho family GTPases are molecular switches best known for their pivotal role in the dynamic regulation of the actin cytoskeleton and play key roles in tubular fibrotic reprogramming. RhoB, an early response gene whose expression is elevated by cellular stress, is a less explored member of the Rho family of small GTPases. Interestingly, levels of RhoB were found elevated in the urine of patients with chronic kidney disease, pointing to a possible role for this protein in the pathogenesis of kidney disease. Further, inflammatory cytokines can upregulate RhoB in endothelial cells and macrophages.

Purpose: To investigate the alteration of RhoB expression induced by pathogenic stimuli in tubular cells and study the role of this protein in tubular responses to inflammation.

Hypothesis: Angiotensin II and TNF-α, known mediators of kidney disease, upregulate RhoB in tubular cells through two mechanisms: activation of the NADPH oxidase and/or the ERK signaling.

Methods: Cultured kidney epithelial cells were utilized to assess the expression and upregulation of RhoB by angiotensin II (AII) or TNF-α using Western blotting. The potential role of the NADPH oxidase and ERK signaling pathways in the upregulation of RhoB was investigated using specific inhibitors.

Results: I have validated two antibodies that specifically detected RhoB. Using these, I showed that both TNF-α and angiotensin II upregulated RhoB, although the effects of angiotensin proved not to reach statistical significance. Neither effect was due to NADPH oxidase (NOX) or Erk, since inhibiting these proteins did not alter the effect. Interestingly, inhibiting ERK or NOX appeared to upregulate RhoB, suggesting these may suppress basal RhoB expression.

Conclusion: My results suggest that AII and TNF-α, two mediators that play a role in chronic kidney disease, also upregulated RhoB in tubular cells. The underlying mechanisms, however, are not yet clear, as neither NADPH oxidase nor ERK signaling pathways were involved in this effect. Interestingly, NOX and ERK may function as suppressors of RhoB, which needs further investigation.

K.3: Targeting fetal lung macrophage dysregulation in congenital diaphragmatic hernia with amniotic fluid stem cell extracellular vesicle therapy

Student: Fabian Doktor, Supervisor: Augusto Zani

Background: Congenital diaphragmatic hernia (CDH) is a congenital malformation leading to the herniation of abdominal organs into the thoracic cavity and is associated with pulmonary hypoplasia. Pulmonary hypoplasia is characterized by impaired fetal lung growth, maturation, vascularization, and macrophage enrichment. Although postnatal surgical repair is possible, neonatal morbidity and mortality remain high.

Purpose and Hypothesis: We hypothesize that experimental antenatal administration of amniotic fluid stem cell extracellular vesicles (AFSC-EVs) improves pulmonary hypoplasia via its immune-modulatory properties.

Methods:

Animals: B6.Cg-Tg(Csf1r-EGFP)1Hume/J (=MacGreen), and B6.Cg-Csf1r$^{tm1.1Jwp/J}$ (=macrophage-deficient mice) on a C57BL/6J background were fed on embryonic day 8.5 with olive oil (control) or nitrofen/bisdiamine (fetal CDH). At E16.5, MacGreen dams underwent intraamniotic saline or AFSC-EV injection. At 18.5, pups were harvested, genotyped, and their lungs analyzed.

EV-characterization and tracking: EVs were characterized for size (nanoparticle tracking analysis), shape (transmission electron microscopy) and canonical EV markers (Western Blot). Tracking was performed with MemGlow 640.

Outcome measures: Pulmonary hypoplasia was quantified via H&E (MLI). Macrophage abundance and EV tracking were measured via immunofluorescence (CD68, EGFP, MemGlow). Gene expression was analyzed via RT-qPCR.

Results: Fetal murine lungs secondary to CDH were hypoplastic and showed altered branching morphogenesis (increased MLI, **$p<0.05$**), maturation (decreased *Pdpn* and *Eln* expression, **$p<0.05$**), vascularization (decreased *Vegfr1*, *Vegfr2*, *Enos*, *Epas*, *Cd31*, **$p<0.05$**), and were enriched with macrophages (CD68, EGFP, **$p<0.05$**). AFSC-EVs interacted with fetal lung macrophages, rescued lung branching morphogenesis and decreased macrophage abundance (decreased MLI, CD68 and EGFP, **$p<0.05$**). In macrophage-deficient mice, fetal pulmonary hypoplasia secondary to CDH was absent (MLI, *Pdpn*, *Eln*, *Vegfr1*, *Vegfr2*, *Enos*, *Epas*, *Cd31*, **$p>0.05$**).

Conclusion: This study is the first to demonstrate that AFSC-EVs hold regenerative potential to rescue pulmonary hypoplasia secondary to CDH via its immune-modulatory properties and that macrophage deficiency protects fetal CDH mice from developing pulmonary hypoplasia. These findings suggest the potential of stem cell-based macrophage immunomodulators as a novel therapeutic approach to support normal fetal lung development.

K.4: Sustained release of Sh3-RdCVF improves cone survival in an rd1 mouse and P23H rat model of retinitis pigmentosa

Student: Lia Huo, Supervisor: Molly Shoichet

Background: Rod-derived cone viability factor (RdCVF) is a promising therapeutic protein that could rescue dying cones in retinitis pigmentosa (RP); however, its rapid clearance, limited bioavailability, and the need for repeated injections hinder translation to the clinic. Therefore, there is a need to develop a delivery system that can sustain the release of RdCVF locally and reduce the number of ocular injections required. We previously developed a biocompatible hyaluronan (HA)-oxime hydrogel that displays mechanical and optical properties like that of the vitreous.

Purpose: Here, we designed an affinity-based strategy for the controlled release of RdCVF from HA-oxime, leveraging the interactions between a Src homology (Sh3) domain that we engineered onto RdCVF (Sh3-RdCVF) and Sh3 binding peptides (SBP) immobilized onto HA-oxime.

Hypothesis: We hypothesize that the slow release of Sh3-RdCVF from our SBP-modified HA-oxime hydrogel will improve cone survival in mouse and rat models of RP.

Methods: To determine the tunability of release, HA-oxime was modified with varying molar excesses of SBP to Sh3-RdCVF and *in vitro* protein release was quantified using an ELISA over 14 days. To test our drug delivery system in an *in vivo* model of RP, rd1 mice were injected intravitreally at postnatal day 21 with 1 µL of either Sh3-RdCVF encapsulated in HA-oxime (N=10), Sh3-RdCVF alone (N=10), HA-oxime alone (N=8) or PBS (N=8). Cone function was assessed using electroretinogram (ERG) weekly until 4 weeks post-injection, followed by quantification of cone survival and outer segment health by histology. To validate our delivery system in larger rodents and to demonstrate its gene-agnostic properties, P23H rats were injected intravitreally at postnatal day 150 with 3 µL of either Sh3-RdCVF encapsulated in HA-oxime (N=4), Sh3-RdCVF alone (N=4), HA-oxime alone (N=3) or PBS (N=3) and followed up weekly with the same histological assessments as in the rd1 mice.

Results: Our *in vitro* protein release showed that as the molar excess of SBP in our hydrogel increases with respect to the Sh3-RdCVF protein, the slower the release. Subsequent *in vivo* injection in rd1 mice demonstrated that our slow-release Sh3-RdCVF increases photopic b-wave amplitudes on ERG compared to the three control conditions at 4 weeks post-injection. Whole retinal cone counts and outer segment length were significantly increased with our slow-release RdCVF formulation compared to mice injected with HA-oxime alone, protein alone, or PBS. At 1- and 3-weeks post-injection, Sh3-RdCVF was only detected by Western blot in retinas injected with our slow-release RdCVF, which indicates that the cone rescue seen *in vivo* is indeed due to our hydrogel's ability to retain Sh3-RdCVF at the retina for at least three weeks while a single protein injection is cleared within a week. In P23H rats, cone survival and outer segment length is similarly increased at 4 weeks post-injection, indicating therapeutic efficacy in another model of RP with a gentler rate of degeneration.

Conclusions: Altogether, these results confirm our hypothesis and demonstrate that our affinity-release HA-oxime hydrogel can overcome the short bioavailability of bolus protein injections and increase cone function and survival *in vivo*, whereby the rate of drug release can be controlled with the molar excess of SBP in the gel. Beyond RP, this versatile injectable hydrogel could be explored in other ocular diseases and circumvent repeated intravitreal injections.

K.5: DialySnake: Safety and efficacy in removing intraluminal fibrin plugs in peritoneal dialysis catheters

Student: Ria Khan, Supervisor: Monica Farcas

Background: Approximately 10% of peritoneal dialysis (PD) catheters become obstructed with intraluminal fibrin plugs (IFPs) within 5 years, posing a life-threatening emergency. Saline flushes with fibrinolytic agents and guidewire manipulation often fail, and emergency surgery is ultimately required, costing $25,000 per patient and exposing patients to potential surgical and post-surgical complications.

Purpose: We developed the DialySnake, a novel, non-invasive tool with the aim of removing IFPs at the bedside in a clinical setting, eliminating the need for surgery. It costs $20 to manufacture and successfully unclogged catheters within 5 minutes in benchtop testing.

Hypothesis: Plain X-ray images in the AP view will provide a reliable imaging modality to enable accurate catheter length measurements on photo measure software and the safe and efficient use of the DialySnake *in vivo* to remove IFPs.

Methods: A 66cm Swan-neck double-cuff Coviden PD catheter was surgically inserted into a pig at St. Michael's Hospital vivarium. Plain X-ray images were taken, and catheter lengths were analyzed using Eleif Photomeasure and Imaios Dicom. Measured lengths were compared to the known catheter length to ensure safe DialySnake insertion, preventing exit beyond the catheter and potential organ damage.

Results: 2/25 and 3/45 measurements exceeded 66cm with Eleif Photomeasure and Imaios Dicom, respectively. 43/45 and 42/45 measurements indicated a safe insertion length for the DialySnake.

Conclusion: Plain X-ray imaging in the AP view is a viable modality for guiding safe and efficient DialySnake use, offering a cost-effective, minimally invasive alternative to emergency surgery for obstructed PD catheters.

K.7: Is blood still necessary for normothermic machine perfusion? Evaluating blood-free pancreas perfusion in a porcine transplant model

Student: Catherine Parmentier, Supervisors: Markus Selzner

Background: The pancreas is the most frequently discarded organ for transplantation due to concerns about viability. Normothermic machine perfusion (NMP) has emerged as a strategy to assess and enhance organ viability prior to transplantation. NMP traditionally relies on blood-based perfusates or oxygen carriers, posing logistical challenges. Our previous work demonstrated the feasibility of 6-hour blood-free NMP in discarded human pancreases, showing comparable outcomes to blood-based perfusion. This study extends these findings by evaluating blood-free perfusion in a porcine transplantation model.

Purpose and Hypothesis: This study aims to evaluate and compare the effects of blood-free normothermic perfusion and blood-based perfusion on pancreatic graft function, viability, and post-transplant outcomes in a porcine model.

We hypothesize that blood-free NMP will maintain pancreatic graft function, viability, and post-transplant outcomes comparably to blood-based perfusion.

Methods: Four porcine pancreases with minimal warm ischemia and 2-hour cold ischemia time were perfused for 3 hours using a blood-free perfusate, and four were perfused using a blood-based perfusate. Grafts were subsequently transplanted, with all recipients surviving until the endpoint (Postoperative day 3, POD_3). One blood-free perfusate case was excluded due to graft thrombosis, and one blood-based due to perfusion-related technical issues. Postoperative assessments included amylase, lipase, LDH, and glucose tolerance testing.

Results: Histological evaluation revealed similar findings in both groups. Mild to moderate parenchymal and fat necrosis with mild edema were observed in both groups post-perfusion. At POD_3, mild to moderate necrosis and edema persisted, along with reactive/regenerative changes, suggesting ongoing repair.

Recipients of blood-free perfused grafts exhibited higher mean amylase, lipase, and LDH levels postoperatively. However, one case exhibited markedly elevated enzyme levels while remaining clinically asymptomatic, suggesting it may represent an outlier. The glucose tolerance test performed on POD_3 demonstrated comparable glucose regulation between the groups, with no statistically significant difference ($p=0.49$).

L: Cancer

L.2: EX-CIPN: A phase I trial of an exercise-based rehabilitation intervention to treat persistent chemotherapy-induced peripheral neuropathy (CIPN)

Student: Eric Antonen, Supervisor: Jennifer Jones

Background: Chemotherapy-induced peripheral neurotoxicity (CIPN) is a prevalent adverse effect of chemotherapy agents that can persist for months or years post-treatment. CIPN is present in about 2/3 of patients who receive neurotoxic chemotherapy. Exercise-based rehabilitative interventions have shown promising results in improving CIPN-related outcomes, but more research is needed.

Purpose and Hypothesis: In response, we developed an innovative remotely delivered exercise-based rehabilitation program called EX-CIPN for cancer survivors with persistent CIPN. We aim to determine if the EX-CIPN program is feasible, acceptable and safe for these patients and describe the effects of the program on clinical outcomes. We hypothesize that the EX-CIPN program will be feasible, acceptable, and safe for cancer survivors with persistent CIPN.

Methods: Phase I single-center, multi-method, pilot study (n=40). Eligibility: ≥ 18-years, who are experiencing CIPN symptoms for ≥6 months post-chemotherapy. All participants will receive the EX-CIPN intervention, a 10-week exercise-based rehabilitation intervention designed to target CIPN symptoms and related functional impairments. The primary outcomes are feasibility, acceptability, and safety of the program. To obtain a preliminary estimate of the effects of EX-CIPN, participants will also be asked to complete questionnaires (pain, CIPN symptoms, CIPN related disability) and physiologic assessments at T_1 (baseline), T_2 (10 weeks after start of program) and T_3 (3 months post-intervention).

Results: To date, the study has 75 referrals with 30 eligible, 27 consented, and 13 ineligible. Out of the active participants (n=23), 23 have completed T_1, 13 have completed T_2, and 4 have completed T_3. Updated data will be presented.

Conclusion: CIPN is a common and potentially debilitating adverse effect of neurotoxic chemotherapy for which there are very limited proven treatment options. Effective symptomatic treatment strategies for CIPN are urgently needed. This is the first study to test an innovative, remotely delivered, exercise-based rehabilitation intervention for cancer survivors with persistent CIPN and the results will help to inform future program revisions and the design of a Phase II study.

L.3: Identifying the molecular signature of infiltrating edge cells in glioblastoma as drivers of tumour invasion and recurrence

Student: Alyona Ivanova, Supervisors: Sunit Das

Background: Glioblastoma (GBM) is the most common malignant brain tumour in adults. Despite extensive research, there haven't been remarkable gains in resolving the seeds of glioblastoma recurrence, and the outcomes for many patients suffering from this devastating disease remain poor. Complete tumour resection in GBM patients is not possible. Residual therapy-resistant cells drive tumour recurrence and infiltrative expansion. Our knowledge on GBM heterogeneity is mostly restricted to the surgically resectable tumour core, while the functional characterization of tumour cells at the infiltrating edge remains largely elusive due to the presence of normal functional brain tissue in the peritumoural lesion. Edge-derived cells exhibit larger capacity for infiltrative expansion and are the main drivers of treatment failure and tumour recurrence, making them action targets for novel treatment approaches.

Methods: To resolve the transcriptional heterogeneity of GBM within the spatial context, we profiled gene expression of tumour regions selected based on histological features ("edge", "core", and "infiltrating zone") obtained from 4 primary and 2 matched pairs of primary/recurrent IDH-WT GBM patients at single-cell resolution with Visium HD.

Results: We show that infiltrative cells are spatially segregated and are characterized by regionally shared distinct transcriptomic signatures which define their cell state and identity. We complement non-spatial leiden clustering approach with BANKSY spatial clustering to augment the features of each cell with both an average of the features of its spatial neighbors along with neighborhood feature gradients. Using pathologically annotated H&E images integrated with spatial gene expression, we identify patterns related to tissue structure and identify transcriptional programs that promote invasiveness and underly disease recurrence in GBM. To further characterize invasive cells at the normal brain-tumour boundary, we identify top spatially variable genes in this cell population using unsupervised cell phenotyping. Upregulated DEGs of tumour edge cells are significantly associated with chemical synaptic transmission, and nervous system development. These modules represent tumour cell hijacking of neuronal programs as described in the context of glioma-neuron synaptic communication and formation of neurite-like tumour microtubes. Upregulation of ion regulation transport at the tumour periphery indicates enhanced neuronal activity and excitability driving infiltrating growth.

Significance: Identifying biomarkers that are specific to malignant edge-derived cells may serve as new diagnostic feature that would help assess treatment response before or within early phases of therapy and allow for individual tailoring of the treatment plan to slow disease progression.

L.4: Investigating dronedarone and PD-1 checkpoint inhibition as a combined therapy for triple-negative breast cancer

Student: Andrew Kennedy, Supervisor: Katarzyna Jerzak, Hon Leong

Background: Triple-negative breast cancer (TNBC) is a molecular subtype of breast cancer that is generally described as highly aggressive and prone to metastasis. Additionally, it has proven difficult to selectively target compared to the other molecular subtypes of breast cancer because it is independent of the receptors (estrogen, progesterone, human epidermal growth factor) that the other subtypes of breast cancer (luminal A, luminal B, $Her2^{+}$) are dependent on. One putative angle is to target the PD-1 receptor expressed on the outer membranes of the cancer cells. This receptor is generally upregulated in TNBC cells compared to the other breast cancer subtypes. Additionally, increased potassium ion concentration in the tumor microenvironment may interfere with adaptive immune responses to cancer. Upon further investigation, the FDA-approved potassium channel inhibitor dronedarone has demonstrated an inherent ability to induce apoptosis in multiple breast cancer cell lines and an orthotopic mouse model.

Purpose: To develop a treatment option that more selectively targets TNBC, a highly lethal cancer subtype.

Hypothesis: The combination of a potassium channel inhibitor and a PD-1 inhibitor synergize to target TNBC.

Methods: We tested the innate cytotoxicity of various potassium channel inhibitor drugs against a variety of TNBC cell lines *in-vitro*. Subsequently, we tested dronedarone's effectiveness in chick chorioallantoic membrane and syngeneic mouse models engrafted with TNBC cells.

Results: So far, the drugs have demonstrated modest effectiveness *in-vitro*. Furthermore, they have shown limited effectiveness and synergy with immunotherapy *in-vivo*.

Conclusions: Dronedarone and PD-1 inhibition combination therapy do not demonstrate sufficient synergy to treat TNBC.

L.5: Modern hormonal contraceptive use and breast cancer risk in women with a pathogenic variant in *BRCA1* or *BRCA2*

Student: Anita Rajkumar, Supervisors: Joanne Kotsopoulos

Background: Oral contraceptive use is associated with an increased risk of breast cancer among women with a pathogenic variant (carrier) in the *BRCA1,* but not the *BRCA2* gene. To our knowledge, there are no studies that have assessed whether an association exists between other types of contraceptive methods (e.g. IUDs, implants, injections) and breast cancer risk.

Purpose and Hypothesis: To evaluate the association between methods of contraceptives and breast cancer risk in *BRCA1* or *BRCA2* carriers. I hypothesize that modern contraceptives including IUDs, implants and injectables will be associated with an increased risk of breast cancer among *BRCA1* and *BRCA2* carriers.

Methods: This is a prospective analysis of *BRCA* carriers enrolled in a longitudinal study with detailed data collection on various exposures, screening practices, and health outcomes at baseline and every two years thereafter. Women are asked to report history of contraceptive use, including start/end year, duration of use, medication name and method of administration. Cox proportional hazard models adjusted for age were used to model the association between contraceptive method and breast cancer incidence.

Results: A total of 4,626 women with a *BRCA1* (n=3,574) or *BRCA2* (n=1,052) mutation were eligible for inclusion (mean age 56 years). Of the 3,171 (68.55%) who reported ever contraceptive use, oral contraceptives were the most frequently used method (n= 2,968; 64.16%), followed by IUDs (n=114; 2.46%), injectables (n=90;1.95%) and implants (n=50; 1.08%). After an average of 8.10 years of follow-up (0.76-28.52), there were 585 (12.65%) incident cases of breast cancer, 384 (65.64%) in ever users vs. 201 (34.36%) in never users (p<0.0001). Oral contraceptive (HR=1.01; 95% CI: 0.94-1.07; P= 0.98) and implant (HR=1.04; 95% CI: 0.79-1.35; P= 0.79) use was not significantly associated with breast cancer risk. However, a significantly increased risk was reported among IUD (HR=1.26; 95% CI: 1.07-1.48; P= 0.005) and injection (HR=1.41; 95% CI: 1.09-1.82; P= 0.009) users compared to never users. Multivariate analyses stratified by *BRCA* mutation status and other factors are ongoing.

Conclusion: IUD and injection use was associated with an increased breast cancer risk in *BRCA1* and *BRCA2* carriers. Given the early age of contraception initiation, it is important to be able to provide evidence-based recommendations to *BRCA* carriers that reflect modern methods and formulations.

L.6: Functional modeling of heterogeneity in pediatric ependymoma

Student: Alexandra Riemenschneider, Supervisors: Vijay Ramaswamy, James Rutka

Background: Ependymoma (EPN) is the third most common brain cancer of childhood, and a major cause of morbidity and mortality. Although historically thought to be a single entity, recent genomic studies have shown that despite looking morphologically identical, molecularly they are driven by a wide variety of oncogenic fusions on chromosome 11, involving *YAP1* or *ZFTA* fused to *RELA*. There are limited therapeutic options, namely surgical resection and radiation as they are mostly chemotherapy unresponsive, all of which are broad-spectrum and have toxic side effects. Our group recently identified a wide spectrum of fusion proteins beyond YAP1 and RELA, with distinct transcriptomic profiles. A major challenge is modeling this heterogeneity as most of our *in vitro* models express the *ZFTA-RELA* fusion gene, but there are no established models that express the *YAP1-MAMLD1* gene.

Purpose: Currently there is a paucity of human models that can be used for pre-clinical discovery of fusion driven supratentorial ependymoma.

Hypothesis: I hypothesize the expression of the fusion gene alone is responsible for the development of ependymoma cancers in neural stem cells during development.

Methods: The sequence of the full length *YAP1-MAMLD1* or *ZFTA-MAML3* fusion gene with a human influenza hemagglutinin (HA) protein tag were individually cloned into a lentiviral vector harbouring an mCherry reporter and packaged in lentivirus. Human fetal neural stem cells (FNSCs) from gestational week 16.5 and normal human astrocytes (NHA) were individually transduced with each of these plasmids at a 0.1MOI. Cells were flow sorted for mCherry positivity to select for successfully transduced cells. Proliferation was analyzed using the Beckman Coulter Vi-Cell XR cell analyzer. Cells were injected stereotactically into the forebrains of immunocompromised mice and monitored for tumour growth with MRI. We screened cell lines expressing the *ZFTA-RELA* canonical fusion and the *ZFTA-MAML3* novel fusion using an electroporation-based CRISPR knockout screening targeting kinases to determine if fusion status affects response.

Results: Fusion expression was confirmed through the positive detection of the expression of the HA tag. Markers of ependymoma, including epithelial membrane antigen (EMA) and FOXJ1, were detected in *YAP1-MAMLD1*-transduced FNSCs, but not in the parental cell line or those transduced with the empty vector control. Furthermore, *SOX2*, a marker of stemness, is downregulated in FNSCs transduced with the *YAP1-MAMLD1* plasmid, but strongly expressed in the parental and empty vector transduced controls. *YAP1-MAMLD1*-fused cells and the respective controls have been injected into the forebrains of mice and tumour development is currently being monitored. No discernable changes in EMA or FOXJ1 were detected in NHAs. Proliferation was significantly increased with *YAP1-MAMLD1* expression and *ZFTA-MAML3* expression in NHAs. Furthermore, tumours develop in the forebrains of mice within four weeks of injection of NHA cells expressing either the *YAP1-MAMLD1* or the *ZFTA-MAML3* fusion. We see differences in genetic vulnerabilities after a kinase-targeted CRISPR knockout screen, which we are currently validating using the FNSCs as a cell line control. We are using these CRISPR hits as a translational guide to screen drugs to discover more specific and effective therapies.

Conclusions: We have developed the first human pre-clinical models of YAP1-MAMLD1 and ZFTA-MAML3 supratentorial ependymoma, and show fusion dependent responses to therapy. The development of these human models can be used to further investigate the biological underpinnings of ependymoma, and serve as valuable pre-clinical tools to develop novel and specific therapeutic strategies.

L.7: Developing new measures of patient and caregiver satisfaction with care on inpatient palliative care units

Student: Clara Sun, Supervisors: Camilla Zimmermann

Background: Assessing satisfaction with palliative care is key to evaluating clinical programs and improving the provision of care. Although validated measures exist for home and outpatient settings, there has been limited research on satisfaction with care on inpatient palliative care units (PCUs). Measures that are available for palliative inpatients rely on retrospective caregiver reports after the patient's death, or proxy assessments when the patient is too unwell to participate. Thus, existing measures of satisfaction with inpatient palliative care are missing patients' perspectives and caregivers' independent views (rather than proxy assessments) during PCU admissions. To address this gap, we developed the Palliative Questionnaire for Inpatients (PAL-QI) and Caregivers (PAL-QC), each with 59 items, based on our prior qualitative research with PCU patients, families, and healthcare providers.

Purpose and Objectives: This study aims to pretest the PAL-QI and PAL-QC on PCUs with 30 inpatients and 30 caregivers in preparation for validation. Specific objectives include: (1) reducing the measures to approximately 40 items based on importance, relevance and redundancy; and (2) revising the wording and order of items to ensure measures are easily understood.

Methods: Patients and caregivers will be recruited from Ontario PCUs to complete questionnaire packages, consisting of a demographic survey and the PAL-QI or PAL-QC. Our approach follows the guidelines for developing and pretesting patient-reported outcomes by the European Organisation for Research and Treatment of Cancer. The 59-item PAL-QI and PAL-QC each have 58 core statements across six domains, plus one global satisfaction rating question. For each core statement, participants will rate on Likert scales: (1) their agreement with the statement, and (2) the importance of each statement. At the end of each domain and the measure itself, participants will answer open-ended questions about the relevance, understandability, and wording of items. The Palliative Questionnaires will be revised and reduced to approximately 40 items by analyzing response distributions, retaining items based on importance, rewording unclear items, and removing redundant or highly skewed items. Cronbach's alpha will be calculated to assess internal consistency of the measures.

Results and Impact: No results have been obtained yet. The pretested PAL-QI and PAL-QC will be used in a larger validation study with a national patient and caregiver sample and further revised to produce validated 25-item versions. These finalized measures will then be used clinically, in research, and for quality improvement initiatives to measure satisfaction with care on PCUs. Eventually, the measures may be used for the accreditation of PCUs across Canada.

L.8: Comparing the use of whole brain radiation therapy and stereotactic radiation therapy in the treatment of patients with brain metastases

Student: Andrew Youssef, Supervisors: Sunit Das

Background: Radiation therapy (RT) is a cornerstone of treatment of brain metastasis (BM). Historically, melanoma, renal cell cancer, gastrointestinal (GI) cancers, thyroid cancer and sarcomas have been considered to be radioresistant. The advent of stereotactic radiation therapy (SRT) has required reconsideration of these categorizations.

Purpose and Hypothesis: This study aims to test outcomes and radioresistance trends in patients with BM receiving SRT compared to WBRT and compare these trends to classical definitions of radioresistant tumours. We hypothesize that the classical definitions of radioresistance will be challenged through this study and that discrepancies in radioresponse will be identified between SRT- and WBRT-treated cohorts across the studied primary cancer types.

Methods: Using administrative data housed at the Institute for Clinical Evaluative Sciences (IC/ES), we identified patients receiving RT for BM. Patients were categorized based on primary tumour type into breast, lung, radioresistant (melanoma, renal cell carcinoma, thyroid, and sarcoma tumour types), colon/GI and other primary cancer types. Within these categories, hazard ratio (HR) of overall survival (OS) in months was compared between patients receiving SRT or WBRT. Additionally, within the SRT and WBRT groups, HR of OS was compared with each primary cancer category relative to the breast cancer primary group. Finally, an analysis was performed to compare outcomes based on lesion counts within the SRT group, along with patients with lesion counts of the SRT group relative to the whole WBRT group.

Results: Median OS (in months) in patients treated with SRT was breast = 13.9, lung = 9.4, radioresistant = 9.2, colon/GI = 3.6, other = 6.9, compared to breast = 3.1, lung = 3.5, radioresistant = 2.5, colon/GI = 3.7, other = 2.2 in patients treated with WBRT (HR: breast = 0.43, lung = 0.55, radioresistant = 0.34, colon/GI = 0.81, other = 0.44)($p<0.05$ in all groups except colon/GI). Within the SRT group, when compared to the breast primary group, lung, colon/GI, and other had significantly different OS (HR: lung = 1.31, radioresistant = 0.99, colon/GI = 1.96, other = 1.50). Within the WBRT group, only other was found to have a significantly different OS relative to the breast primary group (HR: lung = 0.95, radioresistant = 1.25, colon/GI = 1.00, other = 1.36). When comparing the OS of all individual lesion counts within the SRT group, no significant difference was found. The OS and HR when comparing 1-3, 4-7, and 8-10 to 11+ lesions were 9.3 (HR=0.85), 8.28 (HR=1.03), 5.88 (HR=9.9), and 10.8, respectively. OS was significantly higher for 3 or less lesions (9.27 mos), compared to 4 or more (8.28 mos)(HR=1.21). When comparing the OS of 4 or less lesions (9.13 mos) to 5 or more (10.1 mos) (HR= 1.12), no significant difference was observed. When comparing all patients within the WBRT group to patients with 3 or less lesions within the SRT group, the WBRT group had a significantly worse OS (3.02 mos) relative to patients receiving SRT for 3 or less lesions (HR=2.08).

Conclusion: Our study found discrepancies in patient survival outcomes based on both RT type, along with primary tumour type, warranting further investigation into classical definitions of radioresistance in the context of WBRT vs SRT.

M: Cancer

M.1: Characterizing the consent preferences of participants in a pediatric biobank

Student: Frances Argento, Supervisor: Helen Dimaras

Background & Purpose: The Kids Eye Biobank at the Hospital for Sick Children houses an international collection of biological specimens, images, and clinical data for use in future research. Pediatric ophthalmology patients with a wide range of eye and vision conditions are enrolled in the Kids Eye Biobank.

Establishing biobanks with comprehensive data sets is essential for advancing equitable health research in genomics and precision medicine. Participant characteristics may influence their participation choices. This study aimed to (i) define participant consent preferences and (ii) investigate associations between participant characteristics and consent preferences.

Methods: A broad informed consent model was utilized. Main study participation entailed the storage and sharing of participant data with academic researchers. Participants had additional options, including the sharing of resources with for-profit companies, research to develop cell lines or organoids, and sharing of whole genome sequencing (WGS) data. Participants also made communication decisions, including the desire to be notified of incidental genetic findings or future research studies.

Participant date of birth, diagnosis, gender, race, religion, date of enrollment, consent decision-maker, and consent preferences were collected from the Kids Eye Biobank's records. Chi-Square Test was used to investigate associations between participant characteristics and consent preferences. All findings were interpreted with Kids Eye Biobank patient partners.

Results: Between June 2020 and August 2024, 312 patients were approached and 276 (88%) were enrolled. Of the enrolled participants, 79% had a substitute decision-maker and 64% were diagnosed with a malignant neoplasm affecting the eye. Demographic data was available for 81% of participants: 52% were girls/women, 50% identified as belonging to a visible racial minority group, and 75% reported belonging to a religious group.

Participants with malignant neoplasms (e.g., retinoblastoma, optic glioma) opted in to more research choices compared to individuals with benign neoplasms, including research to develop cell lines ($p = 0.005$) and sharing of WGS data ($p = 0.028$). Participants belonging to a visible racial minority opted in less to research of cell lines ($p = 0.02$) or receive future communications ($p = 0.01$) compared to other participants. No significant associations were identified between age, gender, religion or decision-maker with consent preferences.

Conclusion: Understanding characteristics associated with participant consent preferences may help us refine communication strategies and expand the Kids Eye Biobank population. This is essential for advancing high-impact precision child health research. More research is needed to further unpack the findings of this study.

M.2: Integrated molecular profiling reveals genomic processes underlying tumor differentiation in esophageal adenocarcinoma

Student: Karanbir Brar, Supervisor: Jonathan Yeung

Background: Esophageal adenocarcinoma (EAC) is a highly aggressive tumor with poor outcomes and limited treatment options for patients owing to significant intra-tumor heterogeneity. Tumor differentiation is an independent predictor of prognosis in EAC, with poorly differentiated (G3) tumors having worse survival than well or moderately differentiated (G1/G2) tumors. However, the genomic basis of poor differentiation in EAC is not well understood.

Purpose and Hypothesis: In this study, our aim was to utilize laser-capture microdissection (LCM) to enrich EAC samples for tumor cells to identify the genomic drivers of poor differentiation in EAC. Ultimately, this work will help us identify unique genomic changes that can be targeted for the development of personalized therapies in this challenging disease.

Methods: EAC samples were collected at initial diagnosis and underwent LCM to enrich for tumor cells, followed by whole-genome sequencing (WGS) and RNA-seq. Data were processed through standardized bioinformatic pipelines to identify single-nucleotide variants (SNVs), indels, and copy number states. We used SigProfiler to identify mutational and copy number signatures, and the R package maftools for general analysis of WGS data. All analyses were completed in R 4.4.1 and Python 3.10.

Results: We included a total of n=35 G3 and n=36 G1/G2 samples in our analyses. The mean tumor purity was similar across samples, at 66±17% for G3 tumors versus 70±14% for G1/G2 (p=0.246). After filtering for known cancer driver genes, G3 tumors were enriched in KMT2C mutations, a tumor suppressor involved in regulating chromatin structure through histone methylation; and in deletions of the tumor suppressors CRTC1, ELL, and UPF1 ($p<0.05$, Fisher's exact test). G3 tumors were also enriched in alterations in the TCGA "Chromatin (other)" oncogenic pathway, involving genes associated with chromatin remodeling such as ASXL1 and CTCF ($p<0.05$). In addition, extrachromosomal DNAs carrying focal MYC amplifications were only seen in G3 tumors (n=4/34 samples). Gene set enrichment analysis of RNA-seq data revealed multiple pathways upregulated in G3 tumors, including the KEGG EGF-EGFR-RAS-PI3K oncogenic signaling pathway (nominal p-value <0.001). Furthermore, we identified a subset of tumors (n=17 total, n=13 with differentiation data available) showing complete loss of the X chromosome, which was independently associated with significantly poorer overall survival (Cox HR: 2.35 [95%CI 1.05-5.26, $p<0.05$]). Interestingly, 9/13 of the X-deleted tumors were poorly differentiated (G3), indicating that X chromosome loss might be a driving factor contributing to the more aggressive phenotype seen in G3 tumors.

Conclusions: LCM and integrated analysis of multi-omic sequencing data identified multiple genomic drivers enriched in poorly differentiated/G3 tumors, including events associated with chromatin remodeling and total X chromosome loss. These findings shed light on the molecular correlates of poorly differentiated EAC, and will help pave the way for novel targeted therapies in this disease.

M.3: Genomic-based prediction for pediatric cancer predisposition to understand phenotypic heterogeneity

Student: Kai Ren Chen, Supervisors: David Malkin

Background: Cancer predisposition syndromes (CPS) are conditions with elevated cancer risk. However, their prevalence is likely underestimated, making risk stratification based solely on CPS diagnosis insufficient. Beyond this limitation, incomplete penetrance and recent studies have suggested other contributors, such as in the epigenome and genome, to CPS phenotypic heterogeneity.

Purpose and Hypothesis: Hypothesis Current clinical surveillance protocols for pediatric CPS (PCPS) individuals lack personalization, which is hindered by a research gap in leveraging genomic data for risk stratification, except in limited cases. We **hypothesize** that germline genetic variants influence statistical models (e.g. polygenic risk scores (PGS)) and artificial intelligence (AI) models (e.g. machine learning (ML)) for risk stratification, which will inform more precise clinical surveillance protocols. I aim to use PGS and ML models to improve the risk prediction for PCPS patients, as well as patients with pediatric cancer without a known PCPS.

Methods: I will apply PGS models from the PGS Catalog, to analyze our patients' genomics data and obtain a cancer risk score. The same genomics data will be utilized to train and test ML models, such as support vector machines and random forests, to predict the patients' risk.

Result: In our preliminary analysis, predictions of relapse classification achieved 96% accuracy and a 71% accuracy of differentiating onset before and after 9 years old.

Conclusion: This research will personalize PCPS clinical surveillance protocols by integrating genomic data and predictive modelling, forming a foundation for transforming cancer care for high-risk individuals and guiding future precision oncology efforts.

M.4: A feasibility trial of calm in patients with a new and recurrent diagnosis of advanced ovarian cancer: *Traumatic stress as the primary outcome*

Student: Megan George, Supervisor: Gary Rodin, Stephanie Lhereux

Background: Ovarian cancer ranks eighth globally in cancer prevalence and has the highest mortality rate among gynecologic cancers, with >80% of cases discovered at advanced stages (III or IV). The diagnosis or recurrence may often trigger traumatic stress symptoms (TSS). While these symptoms may peak at diagnosis or recurrence, psychotherapy isn't routinely integrated into standard of care at these crucial timepoints, creating a significant gap in equitable supportive care among patients with advanced ovarian cancer.

Purpose: TSS is common in women with both newly diagnosed and recurrent ovarian cancer. Interventions such as Managing Cancer and Living Meaningfully (CALM) are effective in advanced cancer but their feasibility and acceptability at the time of an ovarian cancer diagnosis and recurrence have not been demonstrated. Moreover, studies have primarily assessed depression and post-traumatic stress disorder in similar populations. However, the prevalence of TSS among patients with ovarian cancer at diagnosis and recurrence has not been previously investigated.

Hypothesis: (i) CALM will demonstrate higher feasibility and acceptability among individuals with recurrent advanced ovarian cancer. (ii) Individuals with a newly diagnosed advanced ovarian cancer will exhibit higher baseline prevalence of TSS.

Methods: Patients ≥ 18 years with newly diagnosed or recurrent ovarian cancer are recruited from the Gynecologic Oncology Clinic at Princess Margaret Cancer Centre in Toronto, Canada. Patients who provide informed consent are offered 3-6 sessions of CALM over 3-6 months. Validated patient-reported measures administered at baseline and at 3 and 6 months assess symptoms of traumatic stress, depression, death anxiety and perceived benefit of clinical care. Feasibility criteria include: >30% accrual of newly diagnosed and recurrent ovarian cancer patients approached over 12-months; ≥64% of participants completing > 3 sessions over 6 months; ≥64% completion of outcome measures at each timepoint; >50% of participants report perceived benefit based on score ≥14 on the Clinical Evaluation Questionnaire (CEQ).

Results: Among 25 participants, we found clinically significant TSS at baseline, in 78% of newly diagnosed and in 56% of recurrent cases. Recruitment rates varied between newly diagnosed and recurrent patients, with 22.5% vs. 61.5%, respectively, consenting to participate. Of the 12 participants who reached the second time point assessment (3 months), all have completed their outcome evaluations, demonstrating strong retention and suggesting CALM's potential as a feasible supportive care intervention at these timepoints.

Conclusion: Preliminary data indicate that it is feasible to initiate CALM at the time of ovarian cancer recurrence, but more challenging at the time of new diagnosis. The higher distress but lower recruitment rates for newly diagnosed patients may reflect their lack of full understanding of the challenges that lie ahead and their focus on initial intensive first-line treatment. The high retention rate in these preliminary results speaks to the acceptability of the intervention. This study will inform the design of a future large RCT.

M.5: Socioeconomic status, use of palliative care, and death at home among patients with cancer before and during the COVID-19 pandemic

Student: Javaid Iqbal, Supervisor: Camilla Zimmermann

Background: The COVID-19 pandemic had a profound impact on the delivery of cancer care, but less is known about its impact on place of death and delivery of specialized palliative care (SPC) at end of life (EOL) and about potential disparities in these outcomes.

Purpose: To examine the association of the COVID-19 pandemic with death at home and SPC at EOL, and to determine whether disparities in socioeconomic status (SES) exist for these outcomes.

Hypothesis: (1) Deaths at home will increase with the start of the pandemic, and there will be disparity in this increase according to SES. (2) Increase in home deaths will be greater among patients receiving SPC at EOL.

Methods: An interrupted time series analysis was conducted, using Ontario Cancer Registry data comprising patients aged 18 years and older, who died with cancer between March 16, 2015 and March 15, 2021. Exposure was the COVID-19-related hospital restrictions starting March 16, 2020. Outcomes were death at home and SPC delivery at EOL (last 30 days before death). SES was measured using Ontario Marginalization Index area-based material deprivation quintiles: Q1 (least), Q3 (intermediate), and Q5 (most deprived). Segmented linear regression was used to estimate monthly trends in outcomes before, at the start, and in the first year of the COVID-19 pandemic.

Results: Of 173,915 patients in study cohort, 145,653 (83.7%) died in the pre-COVID-19 period and 28,262 (16.3%) in the COVID-19 period; 94,746 (54.5%) died at home during the entire study period and 100,462 (57.8%) received SPC at EOL. In March 2020, home deaths increased by 8.3% (95% CI, 7.4%-9.1%), which was less marked in Q5 (6.1%; 4.4%-7.8%) than in Q1 (11.4%; 9.6%-13.2%) and Q3 (10.0%; 9.0%-11.1%). There was a simultaneous decrease of 5.3% (-6.3% to -4.4%) in the rate of SPC at EOL, with no significant difference between quintiles. Patients who received SPC at EOL (vs. no SPC) were more likely to die at home, before and during the pandemic. However, there was a larger immediate increase in home deaths among those who received no SPC at EOL, versus those who received SPC: for patients in Q1, the increase for no SPC vs. SPC was 17.5% vs. 7.6%; for Q3, it was 12.7% vs. 9.0%; and for Q5, the increase in home deaths was significant only for patients who did not receive SPC (13.9% vs. 1.2%).

Conclusions: In this cohort study of decedents with cancer, the COVID-19 pandemic was associated with amplified socioeconomic disparities in death at home and SPC delivery at EOL. Future research should focus on mechanisms for these disparities and on developing interventions to ensure equitable and consistent SPC access.

M.6: Uncovering the underlying mechanisms of oxidative protein folding

Student: Favian Retnavarathan, Supervisor: Marianne Koritzinsky

Background: Cancer is one of the leading causes of deaths, affecting one in five people worldwide. Cancer progression is spurred by hypoxia, a phenomenon of low oxygenation which causes tumor cells further from existing vasculature to exceed the supply of oxygen. Cells are more resistant to treatment as a result. One of the many genes upregulated by hypoxia is Vascular Endothelial Growth Factor (VEGF), an angiogenesis factor which consists of two antiparallel monomers covalently linked by two interchain disulfide bonds. Disulfide bond formation occurs both in the endoplasmic reticulum (ER) and the intermembrane space (IMS) of the mitochondria. Disulfide bond formation is possible through a relay system, comprising of both Protein Disulfide Isomerases (PDIs) and the oxidoreductase ERO1. Substrate proteins are oxidized, forming disulfide bridges and the electrons are shuttled from the protein to the PDI, to ERO1 through the FAD binding domain. Molecular oxygen acts as the terminal electron acceptor for this process, generating reactive oxygen species (ROS). Recent studies have identified the ability of VEGF to form these disulfide bonds independent of oxygen. It is still unclear as to what can act as the terminal oxidant under these conditions in mammalian cells. Identifying the underlying mechanism of this process can both aid in the understanding of cancer progression as well as uncovering potential therapeutic targets.

Purpose and Hypothesis: Through these experiments, we are trying to identify an alternative terminal electron acceptor to assist with oxidative protein folding, as well as understand the underlying mechanism of the disulfide bond relay. I hypothesize that cells make use of a nutrient/metabolite in place of oxygen as a terminal electron acceptor under hypoxic conditions.

Methods: VEGF dimerization was observed using a radioactive pulse chase assay. HeLa cells were seeded on 35 cm glass dishes and were transfected with a plasmid encoding VEGF and a FLAG tag for immunoprecipitation. Media and reagents were placed in the anoxia chamber (0% oxygen). Cells were placed in the anoxia chamber one hour before the start of the experiment. Cells were rinsed with phosphate-buffered saline (PBS) and starved of methionine and cysteine for 30 minutes. Proteins were labelled with 50 uCi of EasyTag EXPRESS S35-Protein Labelling Mix for 15 minutes. Radioactive labelling of protein was halted with chase media (DMEM without FBS). After the end of each chase period, media was collected, and cells were flooded with cold PBS containing 20 mM NEM for free cysteine alkylation. Cells were then lysed with RIPA buffer (150 mM NaCl, 1% NP-40, 0.5% Na-deoxycholate, 0.1% SDS, and 50 mM Tris-HCl, pH 7.5) with Halt protease inhibitor and 20 mM NEM. Both lysate and media samples were immunoprecipitated through incubation with Anti-FLAG Magnetic beads at 4°C overnight with rotation. When specified, reduced samples were treated with 50 mM of DTT. Samples were run on SDS-PAGE. Gels were fixed, stained with Coomassie Brilliant Blue, dried and exposed to a storage phosphor screen (GE Healthcare). Signal was detected using a phosphor imager (Typhoon 9410; GE Healthcare).

Results: Under both normoxic and anoxic conditions, the dimerized form is secreted between 30 minutes to 1 hour. Dimer intensity is highest at 2 hours. Under reducing conditions, we see VEGF migrating at approximately 27 kD. This validates that the bands we see migrating at 54 kD in the non-reducing samples are indeed VEGF in dimerized form. The presence of both monomeric and dimeric VEGF in lysate could indicate that dimerization is occurring slower. Further experimentation is needed to determine if dimerization of VEGF is affected by metabolite/nutrient presence and/or composition in growth media. To conclude, VEGF is confirmed to be capable of oxidative protein folding independent of oxygen.

M.7: Characterizing survival and treatment in synchronous intracranial metastatic disease: The influence of extracranial metastases

Student: Madison Sherman, Supervisor: Sunit Das

Background: Synchronous intracranial metastatic disease (IMD) presents a heterogeneous population with varying clinical characteristics and outcomes in non-small cell lung cancer (NSCLC) and melanoma. While extracranial metastases (ECM) are associated with poor survival, their impact on patients with synchronous IMD remains unclear.

Purpose: To investigate the impact of ECM on clinical characteristics, treatment patterns, and overall survival in patients with synchronous IMD in NSCLC and melanoma, and to determine whether ECM status influences outcomes differently in these two malignancies.

Hypothesis: We hypothesize that the presence of ECM at the time of synchronous IMD diagnosis is associated with poorer clinical outcomes, including shorter overall survival, and distinct treatment patterns compared to patients with isolated synchronous IMD.

Methods: This population-based retrospective cohort study included patients diagnosed with NSCLC or melanoma in Ontario between 2010 and 2019. Demographics, treatments, and survival data were obtained from provincial healthcare records. Kaplan-Meier analysis assessed overall survival (OS) univariately, while Cox proportional hazards models estimated multivariate hazard ratios (HRs) with 95% confidence intervals (CIs). Logistic regression evaluated associations between ECM and clinical characteristics/treatment patterns, reported as odds ratios (ORs) with 95% CIs.

Results: Among 45,352 patients (mean age: 69 years), 85% (n=38,473) had NSCLC and 15% (n=6,879) had melanoma. At initial presentation, 53% had no metastases, 37% had ECM only, and 10% (n=4,700) had synchronous IMD. Among patients with synchronous IMD, 94% (n=4,400) had NSCLC, and most (n=4,431, 94%) also had ECM, while 6% (n=269) had synchronous IMD alone. Patients with ECM were more likely to be male (aOR 1.37) and receive brain radiation (aOR 1.87) or brain surgery (aOR 1.71). Time to systemic treatment was similar between groups, but patients with ECM were more likely to receive stereotactic radiosurgery (SRS) and/or neurosurgery (25% vs. 14%). Overall survival for all patients with synchronous IMD was poor (median 2.9 months, 95% CI: 2.8–3.1), and ECM was associated with significantly worse survival compared to synchronous IMD alone (2.9 vs. 4.0 months; aHR 1.50; $p<0.0001$). Among patients receiving SRS and/or neurosurgery, those with synchronous IMD alone had a substantial survival advantage over those with ECM (19.3 vs. 8.9 months; aHR 1.59; $p=0.01$).

Conclusion: The presence of ECM in patients with synchronous IMD is associated with distinct clinical characteristics, more aggressive treatment, and worse survival outcomes. Even among those receiving SRS or neurosurgery, ECM remains a poor prognostic factor. These findings emphasize the need for stratified treatment approaches, as patients with synchronous IMD may have significantly different survival outcomes based on ECM status.

M.8: Describing the transcriptional subtypes of smooth muscle tumours identified by the RACCOON clustering algorithm

Student: Megan Williams, Supervisor: Rebecca Gladdy

Background: Leiomyosarcoma (LMS) is the third most common histotype of soft tissue sarcoma (STS), comprising about 10-20% of STS cases. LMS presents in sites such as the abdomen, including the retroperitoneum, venous structures, and less frequently of the gastrointestinal tract, extremities, and the uterus. Prognosis can vary by site with the 5-year overall survival (OS) being 20-30%, 60%, and 40% for abdominal, extremity, and uterine sites. Regardless of primary tumor location, metastatic disease in these patients remains the primary point of failure emphasizing the need for identification of high-risk groups. Our group has previously defined 3 molecular subtypes of LMS. While these subtypes have been described, their biological differences are poorly understood. Alternatively, uterine leiomyomas (uLMs) are benign entities which can challenge clinicians in making preoperative diagnoses due to similarities in clinical presentation and radiologic features to uterine LMS (uLMS). Despite pre-operative similarities there are drastic differences in outcome between uLM and uLMS and thus necessitates understanding of this biological spectrum of uterine smooth muscle tumours (USMTs).

Hypothesis: This project aims to address the molecular differences within subtypes of LMS and the transcriptional spectrum of USMTs to identify biological differences which can inform biomarkers for stratification or potentially targetable subtypes.

Methods: Following quality control by a sarcoma pathologist, RNA was extracted from uLM (n=28), STUMP (n=5), and LMS (n=36) fresh frozen samples for bulk RNA-seq. Read count data was inputted into Resolution Adaptive Coarse-to-Fine Clustering OptimizatiON (RACCOON), an unsupervised hierarchical clustering algorithm, which creates a transcriptomic taxonomy per previously established methods (ref). Differential gene expression analysis was done with expected counts which were trimmed mean of mean (TMM) normalized by Edge R v4.4.1 and genes were filtered by those with logFC of ± 2 and adj-pvalue of < 0.05. Gene set Variance Analysis (GSVA) v2.0.2 was used to explore enriched gene sets available at the Molecular Signatures Database (MSigDB) v1.68.0. All analyses were done in R v4.4.1.

Results: Visualization of RACCOON output cluster assignments using UMAPs showed a distinct LMS cluster and a uLM/STUMP/uLMS cluster. Within the large LMS cluster there were 3 subtypes, LMS A, LMS B, and uLMS, which had a predominance of uterine sites. There were signficant differences in OS, EFS, and MFS between LMS subtypes, with LMS B having favourable outcomes. LMS B also showed positive enrichment in mTOR signaling, potentially representing an mTOR sensitive subtype. At the next hierarchical level, the heterogenous uLM/STUMP/uLMS cluster divided into 3 subtypes, one of which was strictly uLMS, represented by LG uLMS. These differed transcriptional to the other uLMS samples in that LG uLMS had negative enrichment in RB and E2F targets and reduced expression of these target genes relative to uLMS. There was no difference in OS or EFS between these uLMS clusters.

Conclusion: The molecular profiling of all sites of LMS showed a distinct uLMS cluster, and significant differences in OS, DSS, and MFS across subtypes. LMS B had positive enrichment in mTOR signaling pathways, supporting LMS B as a potentially mTOR sensitive subtype. The identification of a uLM/STUMP/uLMS cluster demonstrated transcriptional separation of uLMS samples between the initial uLMS cluster and the LG uLMS cluster. Comparisons between these clusters support biological differences in tumorigenesis with no difference in clinical outcomes. This work supports the application of molecular subtyping for LMS and USMTs which may assist clinical outcome and management.

N: Cancer

N.1: Ultrasensitive detection and monitoring of circulating tumor DNA using structural variants in early-stage breast cancer

Student: Mitchell Elliott, Supervisor: Nadia Minian

Background: The presence of circulating tumor DNA (ctDNA) after the initiation of curative-intent therapy in early breast cancer (EBC) is a strong predictor of disease recurrence. Existing ctDNA assays, which predominantly target single nucleotide variants (SNVs), exhibit variable sensitivity and specificity. While increasing the number of SNVs in tumor-informed assays can enhance sensitivity, structural variants (SVs) offer an alternative approach that may provide comparable or improved sensitivity without compromising specificity. SVs, which are associated with genomic instability and tumorigenesis, occur across all cancer types and feature unique tumor- and patient-specific breakpoints throughout the genome. SVs in breast cancer remain underexplored, and their utility for ctDNA detection and monitoring is yet to be fully assessed.

Purpose and Hypothesis: We sought to evaluate the clinical validity of an SV-based ctDNA assay for recurrence monitoring in EBC. We hypothesize that SV-based detection of ctDNA will be a sensitive and specific marker preceding disease recurrence in the adjuvant setting and that on-treatment dynamics will be prognostic.

Methods: The study utilized the tumor-informed Pathlight ctDNA assay (SAGA Dx), employing multiplex dPCR to detect up to 16 (minimum 4) tumor-specific SVs in plasma cfDNA. FFPE tumor tissue with ≥20% tumor cellularity was used for SV fingerprint generation, with WGS performed by SAGA Dx. Germline DNA was used to exclude germline and CHIP SVs. Serial plasma samples were collected at baseline, during treatment, perioperatively, and in follow-up, processed, and stored at –80°C. Patients with EBC of all receptor subtypes receiving neoadjuvant systemic therapy (NAT) at Princess Margaret Cancer Centre were prospectively enrolled between 2016 and 2024. Clinical and pathologic data, including stage, receptor status, treatment, and recurrence outcomes, were extracted from medical records. Clinical recurrence was defined as imaging-confirmed metastatic or local disease, with outcomes updated as of September 30, 2024. The primary endpoint was the association between ctDNA detection and distant recurrence-free interval (DRFI), with secondary endpoints including invasive disease-free interval (iDFI). Statistical analyses evaluated SV burden and ctDNA detection in relation to clinical outcomes, stratified by receptor subtype and stage.

Results: An SV-based ctDNA assay was evaluated in a prospectively collected cohort of early breast cancer (EBC) patients (n=100, 568 timepoints) undergoing neoadjuvant systemic therapy (NAT). The study assessed ctDNA dynamics and lead times to clinical recurrence in the postoperative period. ctDNA was detected in 96% (91/95) of participants at baseline, with a median variant allele frequency (VAF) of 0.15% (range: 0.0011-38.7%), and 10% (9/91) had a VAF <0.01%. Detection of ctDNA prior to cycle 2 (C2) of NAT was associated with an increased risk of distant recurrence (HR: 3.35, 95% CI: 1.02–11.07; p=0.047) and improved residual cancer burden (RCB) prognostication (p=0.041). ctDNA was identified prior to distant recurrence in all cases (100% sensitivity), with a median lead time of 417 days (range: 4-1931 days). These findings validate the clinical utility of ultrasensitive ctDNA detection and monitoring through SVs. Further prospective trials are needed to explore ctDNA-guided treatment strategies.

N.2: Identifying lead compounds for a targeted protein degrader of peroxiredoxin 4

Student: Norman Fu, Supervisor: Marianne Koritzinsky

Background: Pancreatic cancer has an extremely poor prognosis, with a 5-year survival rate of 10%; development of systemic therapies targeting vulnerabilities specific to pancreatic cancer is critical to improve patient outcomes. Peroxiredoxin 4 (PRDX4) is a thiol-dependent peroxidase which has been previously demonstrated to be essential for cancer cell survival and proliferation in pancreatic cancer and several other cancer types. However, depletion of PRDX4 in healthy cells and animals produces mild phenotypes, indicating that a cancer drug targeting PRDX4 would have a favorable therapeutic index. Despite this, no inhibitor of PRDX4 exists; its active site thiol complicates traditional inhibitor development. Targeted protein degraders (TPDs) are an emerging class of drug which can act independently of the active site; TPDs reduce protein abundance by inducing proximity between the protein and an E3 ubiquitin ligase, causing the protein to be degraded by the proteasome. Recently, pelitinib has been reported to act as a TPD of PRDX4, making it a potential lead compound.

Purpose and Hypothesis: We hypothesize that pelitinib degrades PRDX4, and that high-throughput screening will uncover further high-quality PRDX4 binders. The purpose of this project is to contribute to development of a PRDX4-targeting drug by identifying PRDX4-binding compounds that can be constructed into an optimized TPD.

Methods: Multiple cancer cell lines were treated with pelitinib for 8 hours, followed by treatment with EGF for 15 minutes. Whole cell lysates were collected and analyzed for PRDX4 expression by Western blot. *In silico* drug screening for PRDX4 binders is underway; top hits (n=80) will be screened along with the OICR fragment library (n=2000) for their binding capacity to PRDX4 via surface plasmon resonance.

Results: Pelitinib inhibited EGF-induced phosphorylation of EGFR but did not affect PRDX4 abundance in A549 cells; analysis in MCF-7 cells to follow. Structural analysis of PRDX4 identified multiple pockets amenable to ligand binding, indicating that a screen for PRDX4 binders is viable. Recombinant PRDX4 purification and optimization of a screening protocol are underway.

N.3: Aberrant mRNA ribosome loading and translation impairs hematopoiesis in Shwachman-Diamond Syndrome with *DNAJC21* biallelic mutations

Student: Shreya Kanade, Supervisors: Yigal Dror

Background: Inherited bone marrow failure syndromes (IBMFSs) are genetic disruptions of hematopoiesis (HP). In this project, we focus on Shwachman Diamond Syndrome (SDS), a multisystem IBMFS with high morbidity and mortality due to hematopoiesis complications. SDS primarily impacts the bones, pancreas, and brain, and is usually diagnosed in early childhood. SDS patients are at risk of severe infections, anemia, bleeding, and are highly likely to develop leukemia. The only therapy is hematopoietic stem cell (produces all blood cells) transplantation, but radiation and chemotherapy given pre-transplant are highly toxic. Transplant failure is common, and patient life expectancy is reduced to 35 years. Previously, we found that DNAJC21 is mutated in ~10% of SDS patients. DNAJC21 facilitates normal protein production by facilitating the maturation of the large 60S ribosomal subunit for mRNA translation. The role of DNAJC21 in hematopoiesis has not been studied.

Purpose and Hypothesis: This study is the first to investigate the role of DNAJC21 in SDS and will present potential genetic and protein therapeutic targets. Such findings are urgently required to develop efficient therapies. We hypothesize that DNAJC21 is required for balanced translation of mRNA subsets that regulate HP, and for maintaining normal haematopoietic stem cell function. We propose that DNAJC21 loss impairs translation of proteins essential for normal hematopoiesis.

Methods: We used human K562 and TF1 cell lines (represent early haematopoietic progenitors) to perform polysome profiling and isolate mRNA strands associated with each ribosome subunit. Per cell line, we compared the shRNA DNAJC21 knockdown, scrambled RNA control, and wild-type (unaltered) conditions. mRNA from each condition was isolated and sequenced. To identify highly dysregulated mRNA/protein pairs, we are comparing mRNA sequencing data to mass spectrometry (MS) protein data of each cell line. We will analyze significantly aberrantly translated proteins through preliminary functional analyses.

Results: Our previous studies indicate that DNAJC21 reduction impacts hematopoiesis in Shwachman-Diamond Syndrome. In this study, from polysome profiling, DNAJC21-knockdown cells showed reduced levels of mature and actively translating ribosomes as compared to the scrambled RNA control cells. Preliminary mass spectrometry analysis of DNAJC21-knockdown K562 cell lines identified several dysregulated pathways, including downregulation of DNA replication and galactose metabolism pathways, and upregulation of hematopoietic cell lineage, purine metabolism, and SNARE interactions in vesicular transport pathways. Ongoing analysis of mRNA sequencing data is revealing differential mRNA loading and translation in DNAJC21-knockdown cells compared to controls; current investigations are pinpointing significant genes of interest.

Conclusions: Based on our preliminary results, DNAJC21 is essential for regular functioning of hematopoiesis. Final analysis results will indicate novel significant genes that are involved in DNAJC21-related Shwachman-Diamond Syndrome. In future studies, these will be evaluated for their role in SDS pathogenesis and potential therapeutic targeting. Further investigations using patient haematopoietic stem cells and bone marrow stromal cells are required to confirm these results in a clinical setting.

N.4: Education and employment outcomes in survivors of adolescents and young adults (AYA) cancer in Ontario, Canada

Student: Daksha Marfatia, Supervisors: Paul Nathan

Background: AYA with cancer face unique challenges as their cancer often occur during the transition into adulthood. This period includes developmentally important milestones such as completing education, entering the workforce, and building financial resources.

Purpose and Hypothesis: Data gathered in a provincial health study was used to explore whether and to what extent survivors of AYA cancers experience delays or reductions in socioeconomic outcomes.

Methods: This cross-sectional study was conducted in Ontario, Canada using the Ontario Health Study (OHS), a self-report questionnaire, with eligible participants linked to administrative health data Participants were current Ontario residents that participated in OHS between 2011-2018. Among 225620 OHS respondents, AYA cancer survivors were classified by having a self-reported cancer diagnosis between the ages of 15-39 years old. Each AYA cancer survivors was matched to 5 controls drawn from the OHS who did not report having developed cancer prior to age 40 years, matched on age sex, and year of questionnaire completion. Educational and employment outcomes were assessed via multivariable logistic regression between AYA cancer survivors and controls. The impact of cancer diagnosis, treatment, age at cancer diagnosis and other risk factors were assessed within AYA cancer survivors. Educational achievement was defined as a participant's highest educational degree achieved. Employment was defined as being currently employed, or unemployed. Unemployed status did not include those that were students, retired, taking care of home/family, unpaid/volunteer work or those unable due to illness/disability.

Results: 3197 AYA survivors and 15985 matched controls were identified. There were no differences between groups in the proportion that reported high school by age 18 [adjusted odds ratio (OR): 0.60, 95% confidence interval (95% CI): 0.25-1.44), p=0.25]. There were no differences in obtaining an undergraduate or graduate degree when compared to other post-secondary degrees (OR: 0.87, 95% CI: 0.74-1.01, p=0.07). Among respondents who completed university degree, survivors were more likely than controls to achieve a graduate degree rather than an undergraduate degree (OR: 2.12, 95% CI: 1.71-2.64, p <.0001). There were no differences between groups in the proportions currently employed vs unemployed (OR: 0.93, 95% CI: 0.74-1.15, p= 0.4626) or in those working full time versus part time (OR: 1.08, 95% CI: 0.95-1.23, p= 0.23). AYA cancer survivors (n= 298) were significantly more likely to report being unable to work due to sickness or disability compared to controls (n=623) (OR: 2.29, 95% CI: 1.97-2.66, p <.0001).

Conclusions: Survivors of AYA cancer did not have lower educational achievement than matched controls without a cancer history. Although the employment and class of employment (full vs part time did not differ between the groups, AYA cancer survivors were significantly more likely to report being unable to work due to sickness or disability, suggesting that care providers should be aware of this vulnerable subset of survivors.

N.5: Health interdependence in children with cancer & their parents: A multimethod, longitudinal study

Student: Stephanie Nanos, Supervisors: Gary Rodin, Lindsay Jibb

Background and Purpose: A childhood cancer diagnosis is disruptive to families, profoundly and negatively impacting their physical/psychosocial well-being. For children, initial disruptions may arise from intensive treatment, symptom burden, and interference with typical childhood activities. Parents are increasingly expected to assume lead roles in complex care while managing existing responsibilities and facing the constant threat that their child will suffer or die. Despite multiple theories of interdependence in close/familial relationships proposing that stress and coping in parent-child dyads are reciprocal and dynamic, their experiences are often assessed separately. This approach offers an incomplete picture of the factors shaping each dyad member's response to cancer and may limit the development of effective psychosocial support. Thus, we aim to holistically characterize the mutual experience of suffering in children with cancer and their parents.

Hypothesis: A dyad member's (either child or parent) physical/psychosocial symptom burden will predict the other's traumatic stress response.

Methods: This prospective, multimethod study will be conducted at the Hospital for Sick Children (Toronto). Participants will be parents (>18yo) of a child (8-18yo) within 6-months of a new or relapse cancer diagnosis (N=120 dyads). Dyads will self-report valid and reliable measures of physical/psychosocial health (e.g., symptom burden, traumatic stress) at baseline and 3-months. A subset (n=20 dyads) varying in demographic and child disease characteristics will participate in semi-structured interviews about the perceived impact of cancer on the other. Quantitative data will be analyzed using Actor-Partner Interdependence Models and qualitative data with an established integrative technique.

Conclusions: This study will be the first to comprehensively describe the extent to which a child-parent dyad member's health status and experiences affect the other. This understanding will provide needed guidance to the design of family-centered psychosocial care for those affected by cancer, and shape future research and clinical practices.

N.6: Origins of human pancreatic cancer phenotypes

Student: Paul Tonon, Supervisor: Steven Gallinger, Faiyaz Notta

Background: Pancreatic ductal adenocarcinoma (PDAC) was once thought to be a homogenous disease, but gene expression phenotypes reveal its diversity. Multiple subtypes have been identified, raising questions about their origins and development.

Purpose and Hypothesis: We hypothesize that these gene expression phenotypes arise from intrinsic cellular state reprogramming, influenced by developmental processes and tissue injury responses. Understanding these mechanisms could lead to more effective therapies.

Methods: We performed non-negative matrix factorization (NMF) on RNA-seq data from 490 microdissected tumors, identifying four RNA tumor signatures clustering tumors into five groups. Specific primers were designed to amplify the KRAS exon 2 hotspot mutation, allowing us to track single cells harboring the mutation. We also collected scRNA-seq datasets from different stages of normal human pancreas development and performed an unbiased search for tissue lineage programs outside the pancreas using the Human Transcriptome Cell Atlas (HCTA). Additionally, we evaluated models of acinar cell stress using pancreatitis and KRASG12D mouse models.

Results: Phenotypes emerging in non-aneuploid cells were associated with cell injury and occurred before KRAS mutations, indicating early cellular stress responses. In contrast, phenotypes that arose in aneuploid cells were linked to the loss of the epithelial ductal state and appeared after KRAS mutations, coinciding with genomic instability. These expression phenotypes did not mirror the normal pancreas but instead represented lineage programs hijacked from other tissues.

Conclusions: Our findings present the first model describing the inception of human pancreatic cancer phenotypes, providing a new framework for understanding the transcriptional landscape of this disease. This model has broad implications for the development of targeted therapies and improving patient outcomes.

N.7: Enhanced MR-guided radiotherapy and tumor hypoxia reduction with manganese dioxide nanoparticles

Student: Rachel Yang, Supervisors: Michael Milosevic

Background: MR-guided radiotherapy (RT) is increasingly being used to treat patients with cancer. However, most solid tumors contain hypoxia, which causes RT resistance and is associated with poor patient prognosis. T-MX is a manganese dioxide (MnO_2) containing nanoparticle with theranostic properties, producing MR tumor enhancement while simultaneously generating oxygen in the tumor microenvironment. This makes it attractive for both improving the targeting accuracy of MR-guided RT and reducing tumor hypoxia.

Purpose: The purpose of this study is to understand the relationship between T-MX induced MR enhancement and hypoxia reduction and factors that influence efficacy.

Hypothesis: T-MX-induced MR enhancement is correlated with its ability to reduce hypoxia and that its efficacy is modulated by tumor-specific factors.

Methods: MR enhancement and changes in tumor hypoxia following T-MX administration were evaluated in orthotopic cervical cancer ME-180 and patient-derived xenograft (PDX) tumor models. Hypoxia was measured using the hypoxia markers EF_5 and pimonidazole. The intratumoral distribution of T-MX was examined using immunofluorescence.

Results: There was significant MRI enhancement for up to 2 hours following T-MX administration in both tumor models, with peak enhancement occurring at 1 hour. ME-180 demonstrated non-uniform enhancement, predominantly localized to the tumor rim. In contrast, the PDXs demonstrated greater and more uniform enhancement throughout the entire tumor volume. ME-180 tumors were more hypoxic at baseline than the PDXs. T-MX had no effect on tumor hypoxia in ME-180 but significantly reduced hypoxia in PDX tumors. T-MX was spatially distributed close to perfused tumor blood vessels, primarily within stromal regions.

Conclusion: T-MX produces strong, reproducible tumor enhancement, indicating that oxygen is being generated in the tumor microenvironment. Differences in hypoxia reduction following T-MX administration likely reflect intertumoral variability in the initial oxygen demand versus nanoparticle uptake and distribution, the latter depending on tumor-specific factors such as perfusion, stromal content, and necrosis. A greater understanding of the factors that influence the therapeutic efficacy of T-MX will inform the design of a first-in-human, phase I clinical trial currently being developed.

N.8: Investigating the role of QKI in tumor differentiation in esophageal adenocarcinoma

Student: Siyi Zhu, Supervisors: Jonathan C. Yeung

Background: QKI is a splicing factor gene encoding the RNA-binding protein Quaking. Previous studies have shown that it serves as a multifunctional regulator in various tumor progression, while its association with esophageal adenocarcinoma (EAC) has not been reported.

Purpose and Hypothesis: We aimed to investigate QKI's role in the progression of EAC, focusing on its impact on clinical outcomes and potential mechanisms in regulating tumor differentiation.

Methods: Bulk RNA sequencing data was obtained from 73 MOCHA patients and 26 organoids derived from these patients with laser capture microdissection (LCM) utilized to enrich tumor tissues. Samples were separated into two groups based on their QKI expression using K-means clustering. The association between QKI and clinical features such as tumor differentiation and survival rates were studied. Gene-level and transcript-level differential expression (DE) analysis were performed to explore the biological mechanism of QKI. 80 TCGA samples were used as an external validation dataset.

Results: A bimodal distribution of the QKI expression was observed in all three datasets. High QKI was significantly associated with poor tumor differentiation ($p = 0.0043$). Although higher QKI expression exhibited a trend toward reduced survival rates, the difference was not significant ($p = 0.12$). DE analysis showed that EPCAM, an epithelial-to-mesenchymal transition (EMT) gene that plays a crucial role in cancer, was upregulated in the low QKI group.

Conclusions: QKI plays a critical role in the progression of EAC, with elevated expression associated with poor tumor differentiation and reduced patient survival rates. Furthermore, high QKI expression is correlated to decreased EPCAM levels, suggesting a potential regulatory relationship in tumor development.

O: Cardiovascular, Respiratory & Muscoskeletal

O.1: End-to-end MRI segmentation tool for carotid vessel wall and lumen

Student: Aarushi Bhardwaj, Supervisor: Alan Moody

Background: Accurate segmentation of the vessel wall and lumen is crucial for assessing carotid atherosclerosis and stroke risk. While MRI provides excellent soft-tissue contrast, manual segmentation is labor-intensive, taking up to 30 minutes per scan, and is prone to variability between radiologists.

Purpose: This project introduces an AI-powered tool that automates the segmentation process and integrates a user-friendly interface, making AI-assisted analysis more accessible and reliable for clinical use.

Hypothesis: An AI-powered segmentation tool can reduce segmentation time while maintaining high accuracy, improving efficiency and reliability in clinical workflows.

Methods: The pipeline first aligns multicontrast MRI (TOF, T1, MPRAGE) by reslicing and registering the sequences. It then applies a two-step U-Net model: the first network detects the carotid arteries, and the second segments the vessel wall and lumen. Expert-generated manual segmentations served as the ground truth. The model was trained on 7,500 MRI slices from the Canadian Atherosclerosis Imaging Network (CAIN), a multicenter dataset spanning six sites in Canada. It was tested on 1,000 slices from CAIN and further evaluated on an external dataset (SLICE) of 800 slices.

Results:

- CAIN dataset: Dice scores of 0.99 for lumen and 0.85 for the vessel wall.
- SLICE dataset (external validation): Dice scores of 0.85 for lumen and 0.67 for the vessel wall.

Conclusions: The AI-powered tool significantly reduces segmentation time from 30 minutes to 3 minutes per scan while maintaining expert oversight. The tool allows radiologists to view the AI's predictions and make adjustments if needed, ensuring both efficiency and accuracy. Future work will expand the pipeline to identify additional plaque features, such as intraplaque hemorrhage, calcifications, and lipid-rich necrotic cores, further enhancing stroke risk assessment.

O.3: Congenital diaphragmatic hernia in Canada: The first national study on patient demographics and clinical outcomes

Student: Adriana Dekirmendjian, Supervisors: Augusto Zani

Background: Congenital diaphragmatic hernia (CDH) is a devastating birth defect, characterized by herniation of the intraabdominal contents into the thoracic cavity, resulting in pulmonary hypoplasia, postnatal pulmonary hypertension, and cardiac dysfunction.

Purpose/Hypothesis: Although treatment has improved over the past three decades, CDH continues to impart a high morbidity and mortality globally. The variability in antenatal and postnatal care is a critical issue which affects outcomes. Herein we performed the first national cohort study examining the treatment of CDH in all 16 Canadian pediatric surgical centers over a 16-year period.

Methods: Following ethical approval (REB#1000081647), we conducted a retrospective cohort study by interrogating the Canadian Pediatric Surgery Network (CAPSNet) database, which collects data nationally from all 16 pediatric surgical health centers. We queried data collected for infants with a diagnosis of CDH between 2006 and 2022. Data analysis was performed on demographic factors, maternal characteristics, geographic location, management strategies, and clinical outcomes. Cases with an available maternal residence postal code were geocoded and linked to database records utilizing the Postal Code Conversion File (PCCF+).

Results: *Demographics:* Of the 1006 infants with CDH during the study period, 59% were male, and 86% had a left-sided defect. Median gestational age at birth was 38 weeks (IQR 2) and mean birth weight was 2961.9 g. Infants with CDH were born to mothers of a mean maternal age of 30.2 years (±5.5), most of whom did not have pre-existing health conditions, and 32% of which resided in rural locations. *Antenatal Care:* Most patients received a prenatal diagnosis of CDH (76%). Only 1 of the 16 participating centers offered Fetal Endoscopic Tracheal Occlusion. *Postnatal Management:* The median length of NICU stay amongst patients was 20 days (IQR 30). Over the study period, 7% of infants underwent extracorporeal membrane oxygenation (ECMO) for a mean duration of 10.6 days (±7.1), with ECMO-related complications occurring in 63% including organ failure in 38%. *Surgery:* Median time to surgery was 4 days (IQR 5) from birth and 52% had a type B defect (<50% of chest wall with diaphragmatic tissue). Minimally invasive surgery (laparoscopy or thoracoscopy) was performed in 13% of patients. *Outcomes:* The overall mortality rate was 16.5%, not including the 7% of fetuses who were electively terminated. Post-operative morbidities were recorded in 38% of patients.

Conclusions: In this first multicenter, national cohort study, we observed similar patient characteristics and clinical outcomes compared to other large database studies, such as the CDH Study Group. Access to fetal medicine procedures remains limited, and only a few patients underwent minimally invasive surgery postnatally. Interestingly, a relatively high survival rate was achieved despite a low use of ECMO.

O.4: The impact of prostaglandin E2 on fibro adipogenic progenitors

Student: Christina Doherty, Supervisor: Jane Batt

Background/Purpose: Trauma resulting from motor vehicle accidents, gunshot or knife wounds and workplace incidents can lead to peripheral nerve trauma. Peripheral nerve trauma induces skeletal muscle atrophy and fibro-fatty infiltration (FFI). The duration of denervation determines the potential for muscle recovery. Fibro-adipogenic progenitor cells (FAPs) are muscle resident stem cells that differentiate to fibroblasts and adipocytes, mediating FFI. FAPs are critical for muscle repair, but undergo a phenotypic switch with persistent denervation, resulting in pathogenic FFI. The cellular and molecular mechanisms regulating FAPs phenotypic switch remain incompletely defined. The presence of the bioactive lipid Prostaglandin E2 (PGE2) has been demonstrated to have a negative regulation on fibrosis in direct muscle injury, but is poorly studied in long-term denervation. The effect of PGE2 on FAPs proliferation and differentiation has not been studied. Given its role in FFI in skeletal muscle, it suggests PGE2 may regulate denervation-mediated FAPs differentiation and pathogenesis.

Hypothesis: FAPs production of PGE2 modulates FAPs phenotypic switch from pro-regenerative to pathogenic, and modulates the time dependent reversibility of denervation induced skeletal muscle injury, through autocrine and paracrine effects.

Methods: Utilizing the rat tibial nerve transection model, the gastrocnemius muscle was denervated, with the contralateral limb serving as an internal control. FAPs were isolated at 5 and 12-weeks post injury, representing reversible and irreversible denervation injury respectively. FAPs were cultured and treated with varying concentrations of PGE2, and mRNA and protein expression for FAPs proliferation and differentiation was assessed.

Results: Denervated FAPs exhibited elevated PTGS2 (gene encoding PGE2 biosynthesizing enzyme), and decreased 15-PGDH (PGE2 degrading enzyme) mRNA levels at 5-weeks post denervation, indicating the presence of PGE2 at this timepoint. The reverse was seen at 12-weeks. Stimulation of healthy FAPs with 100nM PGE2 demonstrated a 5, 16 and 10-fold decrease in Col1a1, SMA and perilipin-1 mRNA expression respectively. Perlipipin-1 immunofluorescence demonstrated a 90% decrease in NAÏVE FAPs adipogenic differentiation in response to 100nM of PGE2 stimulation in culture. 100nM of PGE2 inhibited adipogenic differentiation by over 98% in FAPs isolated from 12-week denervated gastrocnemius as demonstrated by a decrease in Plin-1 mRNA express

Conclusion: FAPs PGE2 secretion is increased at 5-weeks but resolves by 12-weeks. Exogenous PGE2 on cultured naive FAPs inhibits fibrogenic and adipogenic differentiation.

Additionally, PGE2 supplementation in FAPs isolated from 12-week denervated muscle effectively mitigates the pro-adipogenic phenotype characteristic of these cells. Collectively, these findings suggest that PGE2 may play a pivotal role in modulating the phenotypic transition of FAPs, highlighting its potential as a therapeutic target for modulating FAP behavior in pathological conditions.

O.5: Sleep apnea in paralympic ontario-resident athletes with spinal cord injury (sports)

Student: Abrity Gomes, Supervisor: Julio C. Furlan

Background: Sleep-related breathing disorders (SRBDs), characterized by recurrent breathing interruptions during sleep, are a common secondary medical condition following spinal cord injury (SCI), with instances reported in up to 50% of those with paraplegia[1]. Yet, it is largely understudied, under-recognized, and undertreated in this population.[1-3] Untreated SRBDs are associated with excessive daytime sleepiness, fatigue, depression, anxiety, cognitive impairment, stroke, heart attack and death.[4-7] Recent evidence has shown a high prevalence of SRBDs in professional athletes, significantly affecting their athletic performance.[8-11] However, para-athletes with SCI, who are already at greater risk, are rarely studied in this area, and there is limited research on how SRBDs affects their health, athletic performance, and the effectiveness of available treatments. Continuous Positive Airway Pressure (CPAP) has been shown to be effective in non-disabled individuals in treating SRBDs[12-14], but there is no research to date that has examined the effectiveness of CPAP among para-athletes with SCI and SRBDs in improving their mental health, well-being, and athletic performance.

Purpose: 1) Evaluate the effectiveness of CPAP in improving psychosocial and cognitive outcomes (e.g. fatigue, mood, cognition, work and social participation, and quality of life) and athletic performance among para-athletes with SCI who have moderate-to-severe SRBDs. 2) Assess the experience and perspectives of athletes with SCI who undergo CPAP to better understand their challenges related to post-SCI SRBDs and CPAP through semi-structured interviews.

Hypothesis: We hypothesize that using CPAP to treat high-performance athletes with SCI and moderate-to-severe SRBDs will significantly reduce their fatigue, depressive symptoms, anxiety, and cognitive impairment, while improving their work, social participation, quality of life, and athletic performance.

Methods: This pilot study will include para-athletes with any level or severity of SCI who play high-performance wheelchair sports. Home-based sleep apnea testing (ResMed ApneaLink Air) will be used to confirm moderate-to-severe SRBDs. Eligible participants will complete 4 months of CPAP therapy, initiating the single-arm clinical trial (n=15, power = 0.8, a=0.05)[15]. **Participants will complete pre- and post-assessments of psychosocial, cognitive, and sports performance using various questionnaires and laboratory-based measures. The study will conclude with semi-structured interviews.** Statistical analysis will include Wilcoxon signed-rank or paired t-tests for continuous data, Fisher's exact test for categorical variables (significance at $p<0.05$), and thematic analysis with NVivo for qualitative data[16].

Results: The study is currently in the recruitment stage, with seven participants enrolled. Three participants with moderate-to-severe SRBDs have initiated CPAP therapy (ongoing), with a mean age of **51.00 ± 12.77 years**, BMI **29.03 ± 3.81 kg/m^2**, time since SCI **25.33 ± 14.47 years**; all are male (**100%**). In contrast, participants with none-to-mild SRBDs have a mean age of **35.75 ± 5.32 years**, BMI **24.48 ± 5.08 kg/m^2**, and time since SCI **11.67 ± 3.79 years**, with a sex distribution of **50% male**. The mean AHI is **39.67 ± 37.23** in the CPAP group and **1.93 ± 1.16** in the non-CPAP group.

Conclusion: This study will address a critical knowledge gap on CPAP effectiveness in treating SRBDs among para-athletes with SCI, promoting inclusivity in healthcare. As a pilot study, its findings could inform a larger trial, enhancing athletes' health, well-being, and performance while improving SRBD management. Additionally, it will provide qualitative insights into the psychosocial limitations of SRBDs and the use of CPAP, addressing key service gaps and providing valuable context for future treatment advancements.

O.6: The effects of the active stand test on the cardiopulmonary hemodynamic responses in healthy adults

Student: Josh Gopaul, Supervisor: Susanna Mak

Background: The active stand test is recommended to evaluate syndromes of orthostatic intolerance (OI) such as postural orthostatic tachycardia syndrome or orthostatic hypotension. This test is a non-invasive assessment of heart rate (HR) and blood pressure (BP) during supine rest followed by unsupported standing, which replicates stressors that provoke symptoms experienced by patients with OI. Diagnostic criteria for OI are dependent on both magnitude and timing of changes in HR and BP, which alone offer incomplete insight into cardiovascular function. There is evidence that orthostasis acts as both an "unloading" stimulus to preload estimated by intracardiac filling pressures and stroke volume (SV), and a "loading" stimulus to vascular resistance. However, there is limited invasive hemodynamic data with the active stand test and the central hemodynamic response profiles to orthostasis in healthy individuals are still unclear.

Objective: Describe the relative hemodynamic variable contributions and temporal hemodynamic response profiles to the active stand test in healthy adults.

Methods: We prospectively recruited a cohort of healthy adults (n=18; age=48 ± 18; M:F=10:8). Participants completed an active stand test (5-min supine, 10-min unsupported stand) during right heart catheterization and recorded simultaneous pressure-time waveforms from the right atrium (RAP), right ventricle (RVP), pulmonary artery (PAP), and intermittently in the pulmonary capillary wedge (PCWP) position. HR, BP, pulmonary pressures, mixed-venous oxygen saturations (SvO_2), and vastus lateralis muscle oxygen content (SmO2) were sampled during supine and at 1, 3, 5 and 10 minutes of unsupported standing. Thermodilution cardiac output (CO) was measured at supine and 10 minutes of standing from which SV and systemic and pulmonary vascular resistance (SVR) (PVR) were derived.

Results: The only variable to remain unchanged during prolonged standing was BP (systolic, diastolic & mean) ($p>0.05$). We observed HR continue increasing throughout standing to 1.2-fold ($p<0.001$), with the upper limit of normal ΔHR from supine to 10 minutes of standing at 32bpm (averageΔ ± 2 standard deviations; 14 ± 9 bpm). CO and SV decreased 0.8 and 0.7-fold respectively ($p<0.001$), while SVR and PVR increased 1.3 and 2-fold ($p<0.001$) from supine throughout standing. Additionally, all filling pressures (RAP, RVEDP, & PAWP), pulmonary artery pressures (PASP, PADP, & mPAP), mixed-venous oxygen content (SvO2), and vastus lateralis muscle oxygen content (SmO2) continued decreasing significantly throughout standing ($p<0.001$).

Conclusion: Taken together, our data suggest that the active stand test provides sufficient orthostatic stress to both "unload" and "load" the cardiovascular system in healthy individuals. Standing results in decreased SV and intracardiac filling pressures, suggestive of decreased preload. HR may increase to compensate the fall in SV, although CO is still reduced. Standing also results in increased SVR and PVR which may compensate the fall in CO, while MAP is maintained, mPAP is reduced. The increases in SVR and PVR with standing are suggestive of increased afterload.

O.7: Identifying early predictors of survival after LVAD implantation: A retrospective analysis of INTERMACS 1 and 2 patients

Student: Aliya Izumi, Supervisor: Filio Billia

Background: Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) profiles categorize patients based on the severity of their condition at the time of left ventricular assist device (LVAD) implantation. However, their utility in guiding LVAD bridging strategies and predicting postoperative survival outcomes remains unclear.

Purpose and Hypothesis: This study aimed to determine short-term survival rates between INTERMACS 1 and 2 patients, hypothesizing that INTERMACS profile is an independent predictor of survival at 30 days and 1 year following LVAD implantation.

Methods: A single-center retrospective analysis was conducted for all INTERMACS 1-2 patients who received a durable continuous-flow LVAD between 2006 and 2024. Logistic regression was used to identify predictors of 30-day and 1-year survival. Kaplan-Meier analysis compared 30-day unadjusted survival rates between INTERMACS groups, with censoring for device explant and heart transplantation.

Results: Among the 114 patients included in this study, 34 were classified as INTERMACS 1 (30%) and 80 as INTERMACS 2 (70%). Females accounted for 29% of the cohort, and 32% of patients presented with an ischemic cardiomyopathy. INTERMACS 1 patients were significantly younger on average ($p = 0.03$) and more frequently bridged with temporary mechanical circulatory support (MCS) (38%) compared to INTERMACS 2 patients (5%, $p < 0.0001$). Logistic regression identified INTERMACS Profile 1 as the most significant predictor of 30-day mortality, with INTERMACS 2 patients exhibiting a 4-fold higher odds of survival at 30 days (Odds Ratio [OR], 4.25; 95% confidence interval [95% CI], 1.24–15.15; $p = 0.02$). Bridging with temporary MCS did not influence survival outcomes at 30 days (OR, 0.88; 95% CI, 0.21–4.22; $p = 0.87$) or 1 year (OR, 0.80; 95% CI, 0.21–3.28; $p = 0.75$). Instead, at 1 year, age emerged as the only significant predictor of survival (OR, 0.96; 95% CI, 0.92–0.99; $p = 0.03$). Kaplan-Meier analysis reiterated the survival advantage of INTERMACS 2 patients within the 30 days following LVAD implantation ($p = 0.04$).

Conclusion: Although both INTERMACS 1 and 2 patients present with severe clinical deterioration, these findings suggest that when deciding to implant an LVAD, the most important consideration for short-term survival might be INTERMACS Profile 1 (cardiogenic shock) or Profile 2 (declining on inotropes), followed by the patient's age. While temporary MCS is often employed to stabilize INTERMACS 1 patients before LVAD implantation, these results suggest that it may not effectively bridge the survival gap between the two groups. Further research is warranted to refine patient selection criteria and develop more effective bridging strategies to improve survival outcomes for INTERMACS 1 patients.

O.8: Characteristics and predictors of opioid-associated out-of-hospital cardiac arrest: a retrospective analysis in southern Ontario

Student: Hania Siddiqui, Supervisor: Rohit Mohindra, Steve Lin

Background: Opioids are associated with 10-20% of the 350,000 annual out-of-hospital cardiac arrests (OHCA) in North America and are increasingly being identified as a cause of OHCA. The increasing prevalence of occult opioid-associated out-of-hospital cardiac arrest (OA-OHCA) is

alarming, and there is a need to better understand the characteristics of this patient population.

Purpose: To characterize the demographic, clinical, and resuscitation-related factors associated with occult OA-OHCA and identify predictors that differentiate these cases from non-overdose-related OHCA

Hypothesis: Overdose-related arrests, including OA-OHCA, will exhibit unique characteristics compared to non-overdose arrests.

Methods: We performed a retrospective study of adult OHCA patients attended by three paramedic services in Southern Ontario from 2020-2022. Paramedic data was matched with reports from the Office of the Chief Coroner of Ontario to determine the etiology of the arrest. The etiology of arrest was categorized as non-overdose or overdose, with overdose-related arrests broken into OA-OHCA or non-opioid-related arrests. Descriptive statistics were used to summarize characteristics by etiology. Univariate logistic regression was conducted to identify variables associated with OA-OHCA.

Results: Paramedic services attended to and treated approximately 5412 OHCA cases from 2020-2022. Of these, 1302 cases had no apparent cause of arrest. Coroner reports revealed that 199 (15%) of the 1302 arrests were overdose-related cases, 153 OA-OHCA, and 46 non-opioid-related arrests. The average age of OHCA patients with no apparent cause was 63 (SD = 18); 66 (SD = 17) for non overdose-related arrests and 43 (SD = 13) for overdose-related arrests. For the overdose-related arrests, the average age was 41 for OA-OHCAs and 47 for non-opioid-related arrests. 86% of the OA-OHCAs and 70% of the non-opioid related arrests were male. Variables significantly associated with OA-OHCA (p-value < 0.05) based on univariate analyses included age (OR = 0.92, 95% CI 0.91 - 0.93) male sex (OR = 3.04, 95% CI 1.96 - 4.93), bystander naloxone (OR = 40.82, 95% CI 17.66 - 111.08), ROSC (OR = 2.00 95% CI 1.19 - 3.25), and unwitnessed arrest status (OR = 4.16, 95% CI 2.44 - 7.64).

Conclusion: OA-OHCA are common causes of cardiac arrest without a known etiology. Age and sex differences exist between overdose and non-overdose cardiac arrests, with further variations between opioid- and non-opioid-related arrests within the overdose group. Our findings highlight that OA-OHCAs may represent a distinct patient population with unique characteristics compared to non-overdose arrests. Further work to better identify these patients in the field could lead to tailored treatment and improved outcomes for this patient population.

P: Cardiovascular, Respiratory & Muscoskeletal

P.1: Progressive cyclical loading induces enhanced anterior tibial translation in ACL-deficient cadaveric knees: A model for chronic ACL deficient pathology

Student: Kosaran Gumarathas, Supervisor: David Wasserstein

Background: Anterior cruciate ligament (ACL) injuries are the most common knee injury amongst active people. For various reasons, individuals either do not undergo reconstructive surgery or either miss the injury entirely, leading to chronic ACL deficiency (CAD). A CAD knee presents significant clinical challenges due to a lack of optimal treatment options. There are currently no cadaveric models that mirror the anatomical and biomechanical changes of this condition.

Purpose: This study aims to replicate CAD knee pathology in cadaveric specimens through a progressive cyclical loading protocol. We will develop a standardized approach to simulate the progression of chronic ACL deficiency in cadavers, advancing our understanding of progressive joint deterioration and informing clinical intervention strategies.

Hypothesis: In cadaveric knee specimens, applying a defined progressive cyclical loading protocol will result in anatomical and biomechanical changes that produce at least a 30% increase in anterior tibial translation compared to ACL-deficient conditions.

Methods: Using a within-specimen experimental design, 11 fresh-frozen cadaveric knee specimens will undergo sequential testing phases: baseline intact assessment, ACL transection, and three progressive cyclic loading protocols (900N, 1200N, and 1500N, each at 1Hz for 1000 cycles). The knee will be positioned at 22° flexion with predetermined anterior tibial translations of 10mm, 13mm, and 16mm respectively for each loading phase. The methodology aims to simulate repetitive drop landing forces consistent with ACL injury. A specimen will be deemed as reaching CAD knee status if there is a minimum 30% increase in anterior tibial translation (ATT) during a 750N load application compared to the acute ACL-deficient (transected) state, based on previous magnetic resonance imaging (MRI) studies demonstrating similar translation differences between persons with acute and chronic ACL injuries. A five-way repeated measures analysis of variance (ANOVA) will be employed to assess statistically significant differences in continuous variables (ATT, average contact pressure, center of pressure, and contact area) across the testing conditions. For ordinal data (meniscus grading), the Friedman test will be applied. A priori power analyses were conducted to justify the sample size and ensure sufficient power to detect expected differences.

Results: We anticipate an increase in ATT after the ACL is transected, with further incremental increases as cyclic loading is progressed. We expect to see a higher incidence and more severe tears in the posterior horn of the medial meniscus with increasing cyclic loads. With increasing load, we predict a rise in the average contact pressure within the knee joint, along with shifts in the center of pressure and changes in contact area. These alterations in joint mechanics are expected to reflect the impaired stability and altered load distribution during cyclical loading following ACL transection.

Conclusion: We hypothesize that a progressive cyclical loading protocol would be successful in inducing CAD knee pathology in cadaveric knee specimens. We hope that this preclinical model can pave way for future research on treatment options for this patient population including ACL reconstruction, slope correction osteotomy, and meniscal transplantation.

P.3: Exploring the metabolic effects of 10^{0}C cold static preservation of *human* donor lungs

Student: Miguel Martinez Santos, Supervisor: Marcelo Cypel

Background and Purpose: Fewer than 20% of donor lungs are deemed suitable for transplantation, and approximately 10-25% of transplanted lungs develop primary graft dysfunction (PGD) during the immediate postoperative period. PGD is a significant predictor of chronic lung allograft dysfunction (CLAD), the leading cause of long-term mortality following transplantation. Among the risk factors contributing to PGD, ischemia-reperfusion injury (IRI) is one of the most predictable due to standardized cold ischemic preservation protocols. Consequently, targeting the mechanisms underlying IRI-induced damage has become a critical focus of ongoing research. Hypothermic lung storage is necessary for reducing cellular metabolism and preventing energy depletion. However, traditional ice-storage conditions are limited to 6-8 hours of preservation, and exceeding this time frame consistently causes severe graft damage. Studies as early as the 1990s observed improved lung preservation during static storage at 10°C, prompting recent investigations into the mechanisms behind this phenomenon. Recent studies by our group demonstrated that extended porcine lung storage at 10°C showed better mitochondrial health and superior physiological function upon reperfusion compared to those stored on ice. Metabolomic analyses further revealed that 10°C storage preserves the lipid metabolism and activates carbohydrate-based energy and anti-ferroptosis pathways. However, current data relies solely on animal studies, and species-specific metabolic differences (e.g., vitamin C synthesis in pigs versus humans) necessitate investigation in human tissues.

Hypothesis: The preservation of human donor lungs at 10^{0}C induces a modulation of metabolic and mitochondrial processes distinct from those observed with traditional ice storage.

Methods:

Metabolomic Profiling: An untargeted global discovery panel (>5,000 metabolites) will compare metabolic alterations in lung tissues stored at 10°C versus traditional ice conditions, analyzing post-cold ischemia time (CIT) and post-reperfusion transplant samples.

Mitochondrial Gene Expression: RT-qPCR will quantify transcription levels of key mitochondrial regulatory genes involved in biogenesis, fusion, fission, and mitophagy to assess temperature-related alterations in mitochondrial dynamics.

Mitochondrial Damage Assessment: Circulating cell-free mitochondrial DNA (ccf-mtDNA) levels in post-reperfusion plasma will be measured to evaluate mitochondrial damage and its role as a damage associated molecular pattern (DAMP) in triggering inflammatory responses.

Inflammatory Microenvironment Analysis: Multiplex cytokine assays will assess pro-inflammatory (IL-6, IL-8, IL-1β, TNF-α) and anti-inflammatory (IL-10) cytokine levels to determine the impact of storage temperature on lung tissue inflammation.

Expected Results: In the coming weeks I will obtain my preliminary RT-qPCR and multiplex cytokine results. We expect to see some degree of impairment in the mitochondrial life cycle in the traditional ice storage group, and uncompromised mitochondrial dynamics at 10°C. Additionally, we foresee a reduction of inflammatory cytokines in the tissue microenvironment of the 10°C group.

Conclusions: This research aims to understanding the donor lung graft metabolic adaptations at 10°C that could extend cold static preservation time, leverage the regenerative potential of 10°C, inform therapeutic strategies, and pave the way for lung transplantation as a semi-elective procedure.

P.4: Regional disparities of PEEP-induced recruitability and strain. Insights from experimental and clinical studies

Student: Luca Salvatore Menga, Supervisor: Laurent Brochard

Background: In Acute Respiratory Distress Syndrome (ARDS), regional aeration is gravity-dependent. Positive End-Expiratory Pressure (PEEP) should ideally recruit the lung dorsally while minimizing ventral overdistention, reducing repeated tidal-dynamic strain while minimally increasing PEEP-induced static strain. How this happens and differs within experimental models or clinical subphenotypes is unknown.

Purpose and Hypothesis: To assess how disease characteristics influence regional PEEP effects on recruitment and strain in animal models and in patients.

Methods: We re-analyzed data from previous swine experimental models [19 symmetrical acute lung injury (ALI); 10 asymmetrical ALI], from 20 patients with varied causes of ARDS, and 15 COVID-19 patients. All subjects underwent a single-breath derecruitment maneuver from high to low PEEP. Regional effects of PEEP were assessed using Electrical Impedance Tomography (EIT). Global and regional values of recruitment-to-inflation ratio (R/I); recruitability, tidal-dynamic strain, and PEEP-induced strain were calculated.

Results: Animals with symmetrical ALI had the highest median [IQR] R/I at 1.39[1.04-1.66], followed by ARDS patients 1.06[0.70-1.23], COVID-19 ARDS patients (0.66[0.51-0.98]) and asymmetrical ALI (0.45[0.22-0.85]). The dorsal regions were the most recruitable ($p=0.001$). Higher PEEP decreased tidal-dynamic strain in ventral regions ($p<0.01$) while PEEP increased static strain in all regions. PEEP effects on dorsal tidal-dynamic strain were variable and predicted by the ventral-to-dorsal shift in ventilation normalized by the increases in dorsal EELV ($p<0.001$; $r=0.79$ in patients, $r=0.65$ in animals).

Conclusions: Higher PEEP decreases ventral tidal-dynamic strain but can paradoxically increase it in dorsal regions due to ventral overdistention with minimal recruitment. This can be detected by EIT.

P.6: Diaphragmatic structure and function and association with patient reported outcome measures and physical function post-transplant

Student: Rogih Riadandrawes, Supervisor: Dmitry Rozenberg

Background: Lung transplantation (LTx) is a life-saving procedure with beneficial effects on health-related quality of life (HRQL) and exercise capacity. Respiratory muscle changes contribute to functional limitations pre-LTx, but their association with post-LTx respiratory symptoms, HRQL, and physical function have not been well characterized.

Purpose This study aims to: 1) assess differences in respiratory muscle structure and function, HRQL, and physical function in LTx recipients compared to age and sex-matched LTx candidates; 2) evaluate the relationship between respiratory muscle function and post-LTx outcomes.

Hypothesis: We hypothesize that LTx recipients will have better respiratory muscle structure and function, decreased dyspnea, increased HRQL, and greater physical function post-LTx. Additionally, we hypothesize that respiratory muscle structure and function will be moderately associated with dyspnea, HRQL, and physical function post-LTx.

Methods: Prospective, single-center cross-sectional study of adult bilateral LTx recipients (≥ 3 months post-LTx) with pre-LTx diagnosis of chronic obstructive pulmonary disease (COPD) or interstitial lung disease (ILD), and pre-LTx participants matched for age, sex, and lung

disease. Ultrasound of the diaphragm, physical function (handgrip and neck flexion strength, short physical performance battery [SPPB] and six-minute walk distance [6MWD]), respiratory symptoms (MRC dyspnea and St. George Respiratory Questionnaire [SGRQ] Symptom subscore) and HRQL (Short-Form 36 [SF-36]) were evaluated. Diaphragm thickening fraction (TF) was measured during normal (TFdi-tidal) and maximal inspiration (TFdi-max) with diaphragm force reserve (1-[TFdi-tidal/TFdi-max]) calculated.

Results: 38 LTx recipients (64±8 years, 68% ILD, 32% COPD, 66% male; median 6.3 months post-LTx) and 18 pre-LTx candidates (61±8 years, 61% ILD, 39% COPD, 56% male) were evaluated. Post-LTx participants had greater diaphragm function with a lower resting diaphragm TF (0.21 ± 0.11 vs. 0.35 ± 0.17, p = 0.0157), greater maximal diaphragm TF (0.97 ± 0.50 vs. 0.60 ± 0.24, p = 0.0011), and a higher diaphragm force reserve (0.74 ± 0.17 vs. 0.40 ± 0.24, p = 0.0002) than pre-LTx participants. HRQL, respiratory symptoms, and 6MWD were better in LTx recipients compared to candidates. Multivariable regression showed diaphragm reserve was associated with higher Maximal Inspiratory Pressure (7.94 cmH_2O [95% CI: 2.82 to 13.06], p=0.003) and better SGRQ symptoms (-5.99 points [95% CI: -8.70 to -3.30], p<0.0001) for every 0.1 increase in diaphragm reserve. No significant associations were found between diaphragm reserve and dyspnea, SF-36 PCS, 6MWD, or the SPPB.

Conclusion: Diaphragm function was observed to be better in LTx recipients than candidates and is associated with greater inspiratory muscle strength and respiratory symptoms. This study may help guide implementation of rehabilitation interventions like inspiratory muscle training to enhance outcomes post-LTx.

P.7: Identifying strategies that can be implemented to promote use of Question Prompt Lists: A multiple methods study in the context of preventing premature cardiovascular disease after hypertensive pregnancy

Student: Sara Sino, Supervisor: Anna Gagliardi

Background: 37,000+ Canadian women annually develop high blood pressure during pregnancy (HDP), particularly women of colour, and are at high risk of developing early heart disease (HD). Healthy diet, physical activity and medications can reduce HD risk, however, many women with HDP and clinicians are unaware of HDP-related HD risk and how to prevent it. Prior research has shown that a pre-formed list of questions (QPL) would aid in discussing HDP-related HD risk, but there seem to be unresolved tensions that may be affecting QPL use. By targeting these tensions, we hope to increase awareness and use of a QPL for HDP among women and clinicians.

Purpose/Hypothesis: The main aim of this study is to employ a multi-faceted strategy targeting women, clinicians, and knowledge brokers to identify strategies that could be implemented to support awareness and use of a QPL for HDP. **Objective 1.** Identify ways to increase women's confidence to use the QPL for HDP in published research. **Objective 2.** Re-analyze interviews with women with HDP and clinicians to identify more ways to support QPL use by both women and/or clinicians. **Objective 3.** Interview healthcare professionals that women see during or after pregnancy (e.g., midwives, nurse practitioners) about how they might promote awareness and use of a QPL for HDP.

Methods: Our multiple methods study is comprised of 3 phases. The scoping review will consist of published research on any interventions aimed at improving healthcare help-seeking behaviour among women. The secondary analysis involves reviewing all qualitative interview data from a primary study (including women and varying clinicians), organizing transcript quotes, and mapping to *Communication Accommodation Theory* (CAT) domains. Through this, we will identify the motivations for perceived barriers and enablers of use, as well as suggested dissemination strategies of a QPL for HDP. Lastly, we will conduct qualitative interviews with various healthcare professionals that interact with women experiencing or having experienced HDP, to gain further insight on potential strategies for improving awareness and use of a QPL for HDP.

Results/Conclusions: Several barriers and enablers of use were determined through a pilot test of extracted quotes from women and clinicians, when asked about a QPL for HDP. Barriers included time management, dissemination of information, causing anxiety or stress, and language/health literacy barriers. Enablers included increasing patient participation, addressing knowledge gaps, additional insight on required information, reducing confusion, and providing a foundation for question asking. Preliminary recommendations were also identified when mapping to CAT domains. Some participants suggested healthcare professionals should decide when and what to discuss with patients, the QPL should be translated in multiple languages, reducing clinical jargon, and disseminating the QPL across multiple platforms. Through all 3 phases, we will have explored strategies at the level of the patient, system, and healthcare professional, and integrated these findings that could ultimately encourage use and awareness of a QPL for HDP. Wide dissemination and uptake of the QPL by women with HDP and healthcare professionals across Canada will improve patient-provider communication, heart health and quality of life of thousands of Canadian women with HDP annually.

P.8: Obstructive sleep apnea and hypertension: Examining sex differences and alternative sleep apnea metrics on ambulatory blood pressure

Student: Manraj Virk, Supervisor: Mark Boulos

Background: Obstructive sleep apnea (OSA) is linked to hypertension, as repeated airway collapses lead to intermittent hypoxia, which activates the sympathetic nervous system and raises blood pressure. Being male is a known risk factor for developing OSA; however, it remains unclear if sex modulates the relationship between OSA and hypertension. Additionally, it is not well established if the duration (total sleep time under 90% oxygen saturation, TST90) or the severity (lowest oxygen saturation, $LowO_2$) of nocturnal hypoxia contributes more significantly to elevated blood pressure in hypertensive patients with OSA.

Purpose and Hypothesis: This study investigates relationships between sex, OSA, nocturnal hypoxia, and 24-hour ambulatory blood pressure (ABP) in hypertensive patients. It is hypothesized that males with OSA will have greater systolic and diastolic blood pressure (SBP/DBP) than females with OSA, males without OSA, and females without OSA. It is also hypothesized that higher TST90 and lower $LowO_2$ are associated with greater SBP and DBP.

Methods: Hypertensive patients underwent 24-hour ABP monitoring and sleep studies, which allowed for assessment of hypoxia (TST90 and $LowO_2$), presence of OSA (Apnea-Hypopnea Index (AHI)), anthropometric data (age, sex, BMI), as well as the mean 24-hour, awake, and asleep SBP/DBP. OSA was defined as an AHI $\geq$ 15 events/hour. Linear regression analyses examined associations between OSA and 24-hour, awake, and asleep SBP/DBP in male and female patients while controlling for age. Additionally, the relationships between TST90, $LowO_2$, and blood pressure were assessed while controlling for age.

Results: We examined 29 patients (mean age: 55.9 years; 60% male; BMI: 28.9 kg/m^2; mean AHI: 12.0 events/hour), all of whom were taking either 0, 1, or 2 antihypertensive medications. Among them, nine patients were diagnosed with OSA (mean age: 53.8 years; 56% male; BMI: 32.5 kg/m^2; mean AHI: 28.1 events/hour), while twenty did not have OSA (mean age: 56.9 years; 62% male; BMI: 27.5 kg/m^2; mean AHI: 5.1 events/hour). Linear regression analysis revealed that the presence of OSA was significantly associated with higher 24-hour and awake SBP (β = 11.049, 95% CI [0.782, 21.316], p = 0.036; and β = 24.847, 95% CI [12.641, 37.054], p < 0.001, respectively). However, no significant associations were found between OSA and asleep SBP or any DBP measures. When analyzing males separately, OSA presence remained significantly associated with higher 24-hour and awake SBP (β = 24.285, 95% CI [11.012, 37.559], p = 0.001; and β = 24.847, 95% CI [12.641, 37.054], p < 0.001, respectively), as well as 24-hour DBP (β = 10.334, 95% CI [2.115, 18.552], p = 0.017). No significant associations were observed between OSA and other SBP or DBP measures in males, nor between OSA and any SBP or DBP measures in females. Linear regression analysis also revealed no significant associations between $LowO_2$ and any SBP or DBP measures, or between TST90 and any SBP or DBP measures.

Conclusions: Thus, sex, particularly being male, and the presence of OSA were associated with elevated 24-hour and awake SBP in hypertensive patients, suggesting that sex may modulate the relationship between OSA and hypertension. However, measures of nocturnal hypoxia duration (TST90) and severity ($LowO_2$) were not associated with elevated SBP or DBP. Further research with a larger sample size is required to confirm the modulatory role of sex and to better clarify the impact of nocturnal hypoxia in OSA-related hypertension.

Q: Cardiovascular, Respiratory & Muscoskeletal

Q.2: Diagnostic and prognostic significance of miRNA-15a-5p, 16-5p, and 92a-3p in arrhythmogenic right ventricular cardiomyopathy

Student: Shaylyn Joseph, Supervisor: Robert Hamilton

Background: Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC) is a genetic heart disorder that presents significant diagnostic challenges, particularly in predicting prognosis using current clinical parameters. The identification of novel biomarkers, such as microRNAs (miRNAs), may provide insights into ARVC's complex pathophysiology and improve diagnostic accuracy.

Purpose: This multi-site study aimed to assess circulating miRNA expression in ARVC patients, stratified by five-year event-free survival risk, to explore their potential role as diagnostic and prognostic markers for ARVC.

Hypothesis: Circulating miRNAs, particularly those differentially expressed in ARVC patients, can be utilized to improve risk stratification, and predict disease progression.

Methods: We analyzed blood samples from 102 ARVC patients, 24 Brugada Syndrome (BrS) patients, and 22 healthy controls for the expression of 20 miRNAs using TaqMan quantitative real-time PCR. ARVC patients were stratified by their five-year event-free survival risk. Differential expression of miRNAs was assessed, followed by machine learning-based risk stratification. Genotyping and functional annotation of miRNA targets were also performed.

Results: Six miRNAs were differentially expressed between high- and low-risk ARVC patients. MiR-15a-5p, miR-16-5p, and miR-92a-3p demonstrated strong predictive ability for risk stratification, with miR-15a-5p associated with adverse cardiac events. Comparative analysis revealed elevated miRNA expression in ARVC compared to BrS patients and healthy controls.

Conclusion: This study underscores the potential of circulating miRNAs as valuable biomarkers for improving ARVC diagnosis, risk stratification, and prognostic assessment.

Q.3: *Ex vivo* lung perfusion Steen solution induces cell injury in a cell culture model

Student: Kate Rokoss, Supervisor: Mingyao Liu

Background: Lung transplantation is the only intervention for patients with end-stage lung disease when all other treatments have been exhausted. Unfortunately, the success of lung transplantation is limited by a donor shortage and marginal graft quality. *Ex vivo* lung perfusion (EVLP) is a transformative technology that has allowed clinicians to evaluate and utilize marginal donor lungs. EVLP maintains the lungs at normothermia through mechanical ventilation and circulating perfusate. The most commonly used perfusate, Steen solution, may stably support the donor lung graft during EVLP. However, the formulation lacks adequate nutritional support, antioxidants, and may not effectively support basic cell function during EVLP.

Purpose and Hypothesis: The purpose of this study is to evaluate the effects of Steen solution on basic cellular functions in a cell culture model. We hypothesize that cells exposed to Steen solution, compared to culture medium, will affect basic cellular functions. Identify these defects will help in the design and development of a new EVLP perfusate.

Methods: Human bronchial epithelial cells (BEAS-2B) and human pulmonary microvascular endothelial cells (HPMEC) were cultured to sub-confluence and incubated at 37℃ in Steen solution or culture media (M199 or DMEM) for varying lengths of time (2, 4, 24 and 48h). Basic cellular, metabolic and antioxidant-related mechanisms were measured following incubation.

Results: There were no significant differences in cell viability at 2, 4 and 24h in Steen solution compared to culture media in both cell lines. However, mitochondrial reductive potential was significantly reduced at 2, 4 and 24h in Steen solution compared to culture media in both cell lines. After both 4 and 24h, ATP production was significantly reduced in Steen solution compared to DMEM in BEAS-2B cells. After 4h, mitochondrial membrane potential was significantly lower in Steen solution compared to culture medium in both cell types. Glutathione (antioxidant) levels were significantly depleted in BEAS-2B cells incubated in Steen solution compared to DMEM after 24h. Glutathione peroxidase 4 activity, a critical enzyme that attenuates lipid peroxidation, was significantly decreased in Steen solution after 48h. Related, SLC7A11 protein, an important antiporter involved in glutathione synthesis, was increased in Steen solution after 48h.

Conclusion: The observed rapid and sustained disruption in mitochondrial function suggests inadequate metabolic support from Steen solution. Additionally, lack of antioxidative support in Steen solution may reduce protection against lipid oxidation-related cell death - ferroptosis. Metabolic and antioxidative function may be improved by supplementing targeted nutrients and therapeutics. Based on these results, a new EVLP solution is under development.

Q.4: Isolating local repolarization changes for intra-cardiac mapping using multi-electrode arrays and signal processing

Student: Tasnia Subha, Supervisors: Kumaraswamy Nanthakumar

Background: The current method for estimating action potential duration (APD) during intra-cardiac electrical mapping is measuring activation recovery intervals (ARI) of unipolar electrograms (Uni) that integrate far-field signals. Therefore, optical APD continues to be the gold-standard for assessing local changes in repolarization. However, optical mapping is not feasible in vivo or in clinical applications due to dye toxicity and susceptibility to motion artifacts. Multielectrode array catheters for clinical use have allowed for the innovation of principal component-referenced Uni (Uni^{PCR}), which attenuates far-field contribution in electrical signals. Here we apply this concept to isolate local repolarization gradients.

Purpose: We aim to test the Uni^{PCR} strategy to repolarization assessment and test whether Uni ARI or Uni^{PCR} ARI correlates to optical APD.

Hypothesis: We hypothesized that the attenuation of far-field contribution with Uni^{PCR} will allow for more accurate detection of local changes in repolarization than the traditional Uni ARI method.

Methods: Epicardial mapping using Optrell was performed in four pig Langendorff experiments. We administered lidocaine topically at the center of the electrode array to locally alter repolarization. We compared the changes in ARI from Uni vs. Uni^{PCR} before and after application of the drug. To validate Uni^{PCR} ARI against a gold standard, in a rabbit model, we conducted simultaneous optical and electrical mapping to differentiate far-field contribution from true repolarization changes by comparing optical APD to Uni vs Uni^{PCR} ARIs.

Results: At the four electrodes closest to the application site, the median percent reductions in Uni^{PCR} and Uni ARI were 44.2% and 16.9%, respectively. In contrast, far electrodes showed median percent changes of 12.1% and 11.7%, respectively. A greater difference in percent change near vs. far from the application site was observed in the Uni^{PCR} (32.0%, $p < 0.0001$) compared to the Uni (5.2%, $p = 0.0144$). Uni^{PCR} ARI (AUC-ROC = 0.9) more accurately predicted areas near vs. far from the application site than Uni ARI (AUC-ROC = 0.7). Regarding validation against optical APD90, there is a greater correlation between Uni^{PCR} ARI and optical APD90 (slope = 1.2, $R^2 = 0.5$) than Uni ARI and optical APD90 (slope = 0.4, $R^2 = 0.3$).

Conclusion: Uni^{PCR} is more sensitive to local changes in repolarization than traditional Uni. Thus, Uni^{PCR} is a better candidate for local repolarization gradient assessment, ushering an exciting era of clinical repolarization mapping.

Q.5: Surgical management of Ebstein's anomaly patients: Tricuspid valve repair and replacement

Student: Selina Tang, Supervisor: Osami Honjo

Background: Ebstein's anomaly patients may present with tricuspid regurgitation and a reduced right ventricle function. The degree of these symptoms is associated with mortality and reoperation rates in these patients. Furthermore, the outcomes of surgical interventions such as tricuspid valve repair (TV repair) and tricuspid valve replacement (TV replacement) vary.

Purpose and Hypothesis: The purpose of this study is to analyze the outcomes of surgical interventions in patients who have underwent TV repair or TV replacement. It is hypothesized that patients who undergo TV repair will result in better outcomes due to a more contemporary management, with earlier timing of intervention and improved surgical techniques.

Methods: In this ongoing retrospective study, patients of 10 years and older who had undergone either TV repair or TV replacement from June 1976 to October 2023 were included. Primary outcomes of freedom from mortality and freedom from reoperation were analyzed using Kaplan Meier estimates and log rank test. A descriptive analysis of continuous variables was conducted with median and interquartile range (IQR).

Results: A total of 112 patients underwent TV repair or TV replacement (N=67/45; 60/40%), with a median age of 33.9 years (16.6-47.0) and weight of 66.4kg (53.5-80.0). Patients who underwent TV repair had a median age of 24.6 years (13.4-42.4), whereas those who experienced TV replacement had a median age of 40.6 years (29.7-52.2). 20-year freedom from mortality for TV repair and TV replacement was 83.7% (95% CI 0.67-1.0) and 31.1% (95% CI 0.07-1.0), respectively, P=0.051. 20-year freedom from reoperation for TV repair and TV replacement was 96.3% (95% CI 0.05-0.93) and 55.1% (95% CI 0.11-0.62), respectively, P=0.012.

Conclusion: Patients who had underwent TV repair experienced a higher survival rate and a lower reoperation rate. Further statistical analysis with long term follow-ups and a more comprehensive data collection with functional outcomes will need to be conducted.

Q.6: Advancing lung protective strategies: Real-time monitoring and personalized ventilation in ARDS using EIT and machine learning

Student: Zhangli Wu, Supervisor: Haibo Zhang

Background: Low tidal volume (VT) lung protective ventilation is essential for acute respiratory distress syndrome (ARDS) treatment. However, its one-size-fits-all approach may inadequately address ARDS heterogeneity, increasing the risk of ventilator-induced lung injury (VILI) and increased lung weight. Inappropriate lung strain and compliance are key contributors to VILI, but their reliance on computed tomography (CT) limits dynamic and bedside utility. Electrical impedance tomography (EIT), a non-invasive, radiation-free modality, offers real-time monitoring of ventilatory distribution and correlates well with CT-derived lung mechanics metrics. The data-enriched environment generated by EIT also enables integration with machine learning (ML) for early VILI detection and personalized ventilatory strategies.

Purpose and Hypothesis: Our study aims to: 1) investigate correlations between CT and EIT lung mechanics metrics; 2) establish safe lung strain thresholds for VILI prevention; and 3) build ML models to predict lung weight changes as markers of VILI progression. We hypothesize that EIT can measure lung strain with a safe threshold for VILI prevention, validated against using CT.

Methods: In this study, approved by the Animal Care Committee at Unity Health Toronto, 13 HCl-induced acute lung injury (ALI) rabbit models were mechanically ventilated for 6 hours with varying positive end-expiratory pressure (PEEP) and VT. Continuous EIT monitoring and hourly micro-CT scans were conducted. The nnU-Net automated lung segmentation of micro-CT images quantified CT-estimated lung strain and lung weight changes. EIT metrics were analyzed using Timpel software, ML models were built using EIT data, and statistical analyses were performed as appropriate.

Results: The nnU-Net model, trained on 308 annotated micro-CT images, demonstrated high accuracy, reducing segmentation time from 20.34 to 1.03 minutes ($P < 0.001$). CT-estimated lung strain strongly correlated with EIT-derived lung strain ($R^2 = 0.72$), while CT-estimated VT moderately correlated with EIT tidal impedance changes (ΔZ, $R^2 = 0.45$). EIT-derived lung strain varied temporally, reflecting VILI progression. Lower lung strain with reduced compliance and higher lung strain with increased compliance were protective against VILI. ML models trained on EIT data accurately predicted lung weight changes.

Conclusions: This study demonstrated a strong correlation between CT and EIT lung strain metrics and highlighted the protective role of lung strain in interaction with compliance. The predictive models further underscore the potential of EIT for real-time monitoring and optimizing mechanical ventilation in ARDS.

R: Endocrine & Gastroenterology

R.2: Role of adipocyte necroptosis in obesity & glucose homeostasis

Student: Carmen Chan, Supervisor: Cynthia T. Luk

Background: Fat cell (adipocyte) death is a key event in the development of white adipose tissue (WAT) inflammation, a major driver of obesity-associated metabolic dysfunction. Receptor-interacting protein kinase 3 (RIPK3) is an essential modulator of necroptosis, a mode of regulated necrosis. Necroptosis is indicated in several inflammatory pathologies; however, whole-body RIPK3-knockout mice have worsened metabolic dysfunction. Thus, the role of adipocyte necroptosis remains unclear.

Purpose: We sought to investigate the role of RIPK3-mediated adipocyte necroptosis in obesity and glucose homeostasis.

Hypothesis: Adipocyte necroptosis does not play a critical role in obesity-associated metabolic dysfunction.

Methods: The adipocyte-like 3T3-L1 cell line and adipocyte-specific RIPK3 RIP homotypic interaction motif (RHIM) knockout mice generated using adiponectin-Cre*LoxP* recombination were used as model systems. Mice were placed on high-fat diet for 16 weeks as a model of diet-induced obesity.

Results: We demonstrated that caspase-8, a central regulator of apoptosis, suppresses adipocyte necroptosis. Unexpectedly, despite upregulation of caspase-8 signalling in obese WAT, necroptotic signalling was also upregulated in WAT of mice with diet-induced obesity and positively correlated with body-mass index in human WAT. Adipocyte-specific deletion of the RIPK3 RHIM, which is required for necroptotic induction, did not influence weight gain, adiposity, or glucose homeostasis in mice with diet-induced obesity. *Caspase-8* knockdown in 3T3-L1 adipocytes suppressed adipogenesis, which was independent of *Ripk3*.

Conclusions: Collectively, our findings suggest that RIPK3-mediated adipocyte necroptosis does not play a critical role in obesity or glucose homeostasis. Alternatively, we provide evidence that caspase-8 plays an essential role in adipocyte function, offering insight to the molecular mechanisms underlying obesity and metabolic dysfunction.

R.3: Longitudinal evaluation of material deprivation and glomerular function across adolescence and young adulthood in persons with type 1 diabetes

Student: Antoine Clarke, Supervisor: Farid Mahmud

Background: Few studies have examined longitudinal trends in glomerular filtration rate (GFR) in persons with type 1 diabetes (T1D) over the course of adolescence and early adulthood and described these trends in relation to socioeconomic status (SES).

Purpose: We aim to longitudinally evaluate GFR among adolescents and young adults with T1D using Creatinine- (Cr) & Cystatin C- (CysC) derived estimates of GFR and evaluate differences in eGFR on the basis of material deprivation (MD) quintile groups.

Hypothesis: GFR will remain stable across adolescence and young adulthood, but will differ between MD quintile groups.

Methods: Serum Cr and CysC levels were retrospectively extracted from the AdDIT (2009-2016) and SPOR follow-up (2019-2023) studies. Estimated GFR (eGFR) was calculated using the Chronic Kidney Disease in Children under 25 (CKiD U25) Cr & CysC formulas while postal codes were linked to MD quintiles from the Ontario Marginalization Index 2016 as a proxy of SES. Longitudinal differences were evaluated using linear mixed effects regression controlling for the fixed effects of age, sex, diabetes duration, insulin therapy, BMI and HbA1c.

Results: A total of N=140 individuals with T1D ages 10 to <25 years were evaluated at a median of 6 timepoints (IQR: 4-6). Mean CKiDU25CR levels increased slightly as age increased (β: 0.9ml/min/1.73m2/year; P=0.022). For CKiDU25CysC, a significant linear decrease in eGFR of -3.9 ml/min/1.73m2/year was observed throughout adolescence until the age of 18 (P<0.0001) followed by a stabilization during young adulthood (β: 0.2ml/min/1.73m2/year; P=0.08). Significant longitudinal differences in Cr-derived eGFR were observed between MD quintile groups (β: 9.0ml/min/1.73m2; P<0.0001), while no differences were observed with respect to CKiDu25CysC (β:3.0ml/min/1.73m2; P=0.255).

Conclusions: Estimates of GFR vary across adolescence and young adulthood among individuals with T1D and do not remain stable. Differences in longitudinal GFR trends were observed using Creatinine- vs. Cystatin C-derived eGFR formulas in this age group. Significant differences in eGFR were observed between MD quintile groups using CKiD U25Cr, but not CKiD U25CysC.

R.4: Change in FIB-4 at 1 year predicts liver-related clinical events in patients with metabolic dysfunction-associated steatohepatitis

Student: Matthew Gee, Supervisor: Keyur Patel, Jordan Feld

Background: Affecting approximately 1/3 of adults worldwide, metabolic dysfunction-associated steatotic liver disease (MASLD) is the most common chronic liver disease, with 20% of patients having the more active form, metabolic dysfunction-associated steatohepatitis (MASH). Although histological endpoints are currently used in MASH clinical trials, due to safety, accuracy, and cost concerns associated with biopsy, an alternative non-invasive option is desirable.

Purpose and Hypothesis: We aimed to determine if serial FIB-4 changes can help risk stratify patients. We hypothesized that 1-year changes in FIB-4 versus baseline allow for progressive risk strata to predict liver-related clinical events.

Methods: Data were pooled from 5 large placebo-controlled trials in patients with MASH and advanced fibrosis (NCT01672866, NCT01672879, NCT02462967, NCT03053050, NCT03053063). Patients were excluded if they were missing histology or FIB-4 at baseline or at 1 year. Patients were stratified by baseline FIB-4 (<3.48, ≥3.48) or histology by NASH CRN (F_3 or F_4) and 1 year FIB-4 (<1.30, ≥1.30 to <3.48, ≥3.48; or ↓30%, stable, ↑30%) or histology (<F_3, F_3, F_4). Event risk (%), likelihood ratio (LR) and events per 1000 years of patient follow-up (LRE/1000 PY) were calculated with 95% confidence intervals.

Results: After baseline adjustment, FIB-4 worsening was associated with a higher incidence of LREs and FIB-4 improvement had fewer LREs. Trends were consistent for event risk, LR and LRE/1000 PY. Histology underestimated risk compared to the highest FIB-4 stratum.

Conclusions: These results suggest that FIB-4 changes may be useful as a surrogate endpoint in MASH clinical trials and for patient management in clinical practice.

R.5: Novel therapies for cardiorenal protection in kidney transplant recipients

Student: Mai Mohsen; Supervisor: David Cherney

Background: Kidney transplantation is the best treatment option for kidney replacement therapy, providing significant survival and quality of life benefits compared to dialysis. However, kidney transplant recipients (KTR) experience increased risks of morbidity and mortality compared to the general non-transplant population. Cardiovascular disease (CVD) is the leading cause of death with a functioning graft in KTR. Furthermore, the metabolic conditions following transplant increase the risk of chronic kidney disease and allograft loss, which are significant contributors to CVD and death in KTR. Therapies to mitigate adverse cardiorenal outcomes are lacking in KTR. In non-transplant populations, novel therapies, including sodium-glucose co-transporter-2 inhibitors (SGLT2i) and glucagon-like peptide-1 receptor agonists (GLP1-RA) have demonstrated significant cardiorenal protection. However, their clinical use in the transplant setting is limited by the absence of large outcome trial data. There is a critical need to evaluate the efficacy and safety of these cardiorenal protective therapies in KTR.

Research aim/ hypothesis: To investigate the efficacy and safety of SGLT2i and GLP-1RA monotherapy and in combination in KTR with type 2 diabetes. We hypothesize that SGLT2i and GLP-1RA alone or in combination would be well tolerated and safe in KTR with similar effects to the non-transplant population.

Methods: We conducted a retrospective study of all adult KTR with type 2 diabetes transplanted at the University Health Network and St. Micheal's Hospital after Jan-1-2000 and started on SGLT2i and/or GLP-1RA. KTR with type 2 diabetes who received SGLT2i and/or GLP-1RA after transplantation were matched with KTR who did not receive either medication. Propensity score matching was performed using nearest-neighbor 1:3 matching to equalize the differences in baseline characteristics between users of SGLT2i and/or GLP-1RA and non-users. The matching variables included age, sex, transplant year, body mass index, donor type (deceased/living), eGFR, diabetes medications, and comorbidities. Baseline characteristics including age, sex, comorbidities, donor type, eGFR, BMI and urine albumin-creatinine ratio (uACR) were collected for all study participants. Primary outcomes included the incidence rate of graft failure, total graft failure and all-cause mortality assessed between day 1 after the index date and up to 8 years post-index event. Secondary outcomes included total eGFR slope (i.e., the annual rate of change in eGFR from index date to the end of the follow up period), occurrence of adverse events and change in metabolic variables.

Statistical analysis: Cox-proportional regression analysis was used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for the primary study outcomes. The variables for the regression analysis included recipient age, recipient sex, comorbidities, eGFR at drug initiation, BMI at drug initiation, uACR at drug initiation and donor type. Cumulative risks were generated by Kaplan Meier estimates.

Preliminary results: Between Jan-1-2000 and July-10-2024, 235 patients received SGLT2i, 145 patients received GLP1-RA and 132 patients received both medications. Results are currently being analyzed.

R.6: Bench to bedside: Optimizing the clinical integration of artificial intelligence for enhanced surgical guidance in the operating room

Student: Ariana Walji, Supervisor: Amin Madani

Background: Surgical complications affect over 7 million patients annually, often due to decision-making errors and cognitive biases. To address this, our team has developed an artificial intelligence (AI) model that provides real-time decision support during laparoscopic cholecystectomy—a common abdominal procedure with a risk of bile duct injury. The model generates color-coded overlays on the live video feed to highlight safe and unsafe dissection zones. Before clinical implementation, its safety must be evaluated in the operating room (OR).

Purpose: As a preparatory step for a clinical trial assessing the model's safety, we are conducting a user acceptance testing (UAT) study to compare cloud and edge computing systems for AI deployment in the OR. Determining which system best integrates into existing workflows and supports end-users is key to seamless AI adoption and real-time usability.

Hypothesis: We hypothesize that system design and setup will influence user preference and, ultimately, the selection of the optimal AI deployment system.

Methods: User acceptance is assessed through observational notes, task completion rates, and feedback surveys. Usability is measured using the System Usability Scale (SUS), cognitive and physical workload via the NASA Task Load Index (NASA-TLX), and overall experience through open-ended survey responses.

Results: Preliminary findings suggest a trade-off between usability, cognitive and physical load, and task performance across user groups. Surgeons (n=2) rated the Edge system as more usable (SUS: 76.25 vs. 63.75) and slightly less cognitively demanding (NASA-TLX: 15.84 vs. 16.84), though task completion was higher with the Cloud system (100% vs. 81.82%). Surgical residents (n=2) reported no usability differences (SUS: 61.25 for both) but experienced slightly greater cognitive workload with the Edge system (NASA-TLX: 34 vs. 33). OR nurses (n=6) found the Cloud system more usable (SUS: 64.58 vs. 56.25 for Edge).

Conclusion: These preliminary findings highlight the need to balance usability, cognitive and physical load, and performance efficiency when selecting an AI deployment system for the OR. The final UAT results will guide the choice of the most suitable system, informing a clinical trial that will evaluate the AI model's safety by monitoring intraoperative and postoperative adverse events.

R.7: Analyzing the role of CNV burden on BMI in patients with obesity

Student: Yu Wu, Supervisor: Satya Dash

Background: Obesity significantly contributes to cardiometabolic diseases (CMD), including type 2 diabetes (T2D), dyslipidemia, and coronary artery disease (CAD). While genetics, particularly single nucleotide polymorphisms (SNPs), have been extensively studied in obesity research, emerging evidence highlights the role of copy number variations (CNVs). CNVs involve deletions and duplications of DNA segments, influencing gene expression and phenotypic traits. The impact of common CNVs on body mass index (BMI) in extremely obese populations remains unclear.

Purpose: This study investigates the association between common CNV burden (total length of deletions and duplications) and pre-operative BMI in obese patients who had bariatric surgery.

Hypothesis: We hypothesize that a higher CNV burden (deletions and duplications) is significantly associated with increased pre-operative BMI.

Methods: A cohort of 532 bariatric surgery patients was analyzed. CNV data from microarray analysis were processed using the CNVpartition package in GenomeStudio. Large CNVs (≥10 Kb) were retained for analysis. Multiple linear regression models assessed the relationship between CNV burden and baseline BMI, adjusting for age and sex.

Results: Deletion burden was negatively associated with pre-operative BMI (β = -0.7506, P = 0.000836), and duplication burden showed a similar association (β = -0.47911, P = 0.014). However, low adjusted R^2 values (0.0464 and 0.03707) indicated limited explanatory power.

Conclusions: While statistically significant, the modest effect size suggests that common CNVs contribute minimally to BMI variance in extreme obesity. Future analyses will explore CNV impact on weight-loss outcomes and incorporate clinical predictors to improve model accuracy.

R.8: Identifying how knocking down YAP in adipocytes improves glucose metabolism

Student: Fan Yang, Supervisor: Cynthia Luk

Background: Yes-associated protein 1 (YAP) is a transcriptional co-activator of the Hippo signaling pathway, which regulates cell proliferation, migration, survival, and apoptosis. In addition to being a potent oncogene, recent studies suggest that YAP has an important role in glucose metabolism and adipose tissue biology. Previously, we showed that YAP protein was increased in adipose tissue from humans with and mouse models of type 2 diabetes. To study the role of YAP in adipocytes and glucose homeostasis, we used an adiponectin-Cre loxP recombination system to generate adipocyte-specific YAP knockout mice (*AdipoqYAP-/-*). When fed a high-fat diet (HFD), knockout mice had improved glucose tolerance compared to littermate controls (*AdipoqYAP+/+*), showing that lowering *Yap1* in adipocytes prevents glucose intolerance with metabolic stress. Nonetheless, how adipocyte YAP regulates glucose metabolism remains unclear.

Purpose and Hypothesis: The objective of this study is to identify potential novel mechanisms whereby knocking down *Yap1* in adipocytes improves glucose tolerance. We hypothesize that lowering YAP gene expression improves glucose metabolism by increasing beta-arrestin 2.

Methods: To gain insight into the role of *Yap1* knockdown on the cell transcriptome and functional relevance, RNA sequencing was conducted. RNA was isolated from perigonadal adipose tissue obtained from mice with adipocyte-specific *Yap1* knockdown and littermate controls. Sequencing was performed on an Illumina NovaSeq 6000 instrument (150 cycles). Transcript abundances were estimated and the FPKM value was calculated using StringTie and the R package Ballgown, respectively. Gene Ontology and Pathway analysis were performed with the differentially expressed genes in R, Python or shell environments.

Results: Differentially expressed genes and transcripts were filtered by fold-change (cutoff 1.5), p-value ($\leq$ 0.5) and FPKM ($\geq$ 0.5 mean in one group). As expected, *Yap1* was significantly downregulated in adipose tissue. Notably, β-arrestin 2, a multifunctional adapter protein involved in the internalization, desensitization, and kinase activation of G protein-coupled receptors (GPCR), was also differentially expressed (1.669-fold) with YAP knockout. Moreover, Western blotting conducted on proteins extracted from subcutaneous and visceral fat confirmed that β-arrestin 2 proteins increased in knockout mice versus control mice. This was associated with improved adipose tissue-specific insulin sensitivity demonstrated by increased levels of phosphorylated Akt. Pathway analysis of differentially expressed genes from RNA sequencing also suggested activation of the MAPK signalling pathway. Further work is needed to identify whether YAP may directly or indirectly regulate these pathways involved in insulin response.

Conclusion: This work identifies potential mechanisms whereby lowering *Yap1* gene expression in adipocytes may improve glucose metabolism, such as by upregulating β-arrestin 2. This will help improve our understanding of adipose tissue biology and its role in type 2 diabetes.

S: Population Health & Education

S.1: A descriptive study of the implementation of ECHO chronic pain in Canada: A qualitatuve analysis

Student: Da Beattie, Supervisor: Andrea Furlan

Background: Chronic pain affects 1 in 5 Canadians. In 2019, Health Canada reported that the total cost of healthcare associated with chronic pain was between 38.1 and 40.3 billion and could be up to 50 billion by 2030. ECHO was founded in New Mexico in 2003 by Dr. Sanjeev Arora after noticing a high rate of untreated Hepatitis C in the state. It is an online program that promotes multidisciplinary communication and knowledge transmission through didactics and discussion of complex patient cases over multiple sessions. Implementation of ECHO across various conditions has shown to increase self-reported knowledge in both patients and health care providers, reduce costs related to travel time, and was associated with a reduction in opioid prescriptions. ECHO Pain was brought to Canada in 2014. There are currently 12 ECHO Pain hubs across 5 provinces with focuses on children, pregnancy, and Indigenous health.

Purpose and Hypothesis: The purpose of my research is to describe the adoption of ECHO Pain and evaluate the spread of ECHO Pain in Canada. I aim to understand the history of ECHO Pain in Canada from the perspective of those who adopted it and to determine where ECHO Pain has not spread and why. I aim to publish a descriptive historical paper of ECHO Pain diffusion in Canada and suggest areas where new ECHO Pain hubs are needed.

Methods: I will use the Diffusion of Innovations theory to guide data collection and analysis. I will be conducting qualitative interviews with a senior leader from each hub. Interviews will be recorded with handheld recorders and transcribed.

Results: Not applicable at time of submission. Preliminary results available on poster.

S.2: Effective digital solutions for problem drinking in treatment-seeking people who smoke to reduce the risk of cancer

Student: Anuijan Chandran, Supervisor: Nadia Minian

Background: Clinical guidelines recommend addressing alcohol and tobacco at the same time, but few primary care providers in Ontario offer brief alcohol interventions routinely, and tobacco and alcohol are often treated separately. Digital interventions could help overcome some barriers. While several interventions have aimed to address dual use, a gap remains in identifying behaviour change techniques (BCTs) designed to change or modify causal processes controlling behaviour.

Purpose: Identify effective BCTs that reduce the dual use of alcohol and tobacco to implement in a digital intervention.

Methods: Following Cochrane recommendations, a rapid review to identify effective BCTs for reducing dual tobacco and alcohol use was conducted. We searched academic databases for relevant empirical studies and used a Taxonomy tool to identify effective BCTs. Based on the findings from this review, professionals with expertise in alcohol and tobacco treatment digital interventions and behavioural change were invited to a Delphi study, to evaluate the BCTs identified to provide their perspective and assessment of each technique.

Results: 2076 articles were initially screened, the full texts of 93 articles were screened, and 38 articles were included in this review. Goal setting, action planning, and pharmacological support were the most common BCTs identified. Experts identified appropriate BCTs implementable in a digital intervention through their expertise.

Conclusion: This evidence synthesis summarizes how BCTs can be used to help people quit smoking and drinking. Overall, these results aim to contribute to the optimization of digital solutions for problem drinking in treatment-seeking people who smoke.

S.3: The impact of 2SLGBTQ+ youth community connectedness on cigarette smoking cessation

Student: Idin Fakhrjahani, Supervisors: Michael Chaiton

Background: Members of the 2SLGBTQ+ community face stigma and marginalization that is associated with unique health disparities, including a greater risk of cigarette smoking and younger smoking initiation than non-2SLGBTQ+ people. With 1 in 10 Canadian youth identifying as 2SLGBTQ+ – notably higher than older Canadians – knowledge gaps remain with respect to supporting positive health-related behaviours for this population (e.g., cigarette smoking cessation). While literature regarding 2SLGBTQ+ youth smoking disparities is abundant, smoking cessation has scantly been explored.

Purpose: The purpose of this study was to assess the impact of community connectedness among 2SLGBTQ+ youth on cigarette smoking cessation.

Hypothesis: It was hypothesized that greater 2SLGBTQ+ youth community connectedness would be associated with greater likelihood of smoking cessation.

Methods: Longitudinal data from four timepoints were collected as part of the Expand Project, to better understand the cigarette smoking patterns of 2SLGBTQ+ youth across Canada. A generalized estimating equation was used to assess the impact of community connectedness (5-point Likert scale) on 30-day cigarette smoking cessation events at each timepoint following baseline. 30-day cessation events were defined as not having smoked in the previous 30 days at the present timepoint but having smoked within 30 days at the preceding timepoint. Correlates were controlled for in the analysis.

Results: The study identified an interaction between community connectedness and age, such that 2SLGBTQ+ youth below age ~22 years were less likely to quit cigarette smoking with greater connectedness, but youth above age ~22 years were more likely to quit with greater connectedness. The interaction held when controlling for current vaping, gender identity, sexual orientation, ethnicity, rurality, household income, substance use (i.e., alcohol, cannabis), 2SLGBTQ+ identity centrality, and acceptance of smoker identity.

Conclusions: Community connectedness can be a useful strategy for 2SLGBTQ+ youth to validate their identity and increase their likelihood of smoking cessation. However, age-specific challenges remain for ensuring connection with one's community fosters positive health behaviours (i.e., smoking cessation) instead of negative ones. Future smoking cessation interventions should employ distinct strategies for the youngest youth, who may be struggling to accept their 2SLGBTQ+ identity and thus less likely to quit smoking.

S.4: The effect of de-insuring routine eye exams in Ontario on optometric glaucoma diagnostic billings

Student: Kiko Zi Yi Huang, Supervisors: Ya-Ping Jin

Background: Glaucoma, a leading cause of blindness in Canada and worldwide, is often asymptomatic until advanced stages. Early diagnosis through routine eye exam (REEs) by optometrists (ODs) play a crucial role in glaucoma detection. In 2004, Ontario became the last Canadian province to de-insure publicly funded REEs for individuals aged 20-64, with exceptions for those on social assistance or with specific conditions, including glaucoma. Evidence on the impact of this policy change on glaucoma detection by ODs is lacking.

Purpose: To assess the effect of REE delisting on new glaucoma billings submitted by ODs.

Hypothesis: We hypothesize that the 2004 de-insuring of REEs (referred to as major eye exams in optometric billings to Ontario Health Insurance Plan or OHIP) resulted in a significant decrease in the number of glaucoma diagnostic billings submitted by optometrists for the policy-affected age groups (20-39, 40-64). Further, we expect that in the policy unaffected 65+ group, optometric glaucoma billings before and after 2004 will remain stable.

Methods: We analyzed OHIP billing data from 1998-2019 to determine (1) the annual number of patients with a new glaucoma billing (diagnostic code 365) by ODs per 10,000 population and (2) the percentage of new glaucoma billings by ODs among all new glaucoma billings by both ODs and ophthalmologists. Analyses were stratified by OHIP-defined major exams by ODs and demographics (age group, urban/rural residency and income quintile). Changes in billings before vs after the 2004 policy change were statistically tested using segmented regression analysis.

Results: In policy affected groups, the number of individuals with a new glaucoma billing by ODs at major exams per 10,000 population decreased significantly from 2004 to 2005: 10.4 (95% CI: -10.9, -9.9; p<.0001) for the 20-39 group and 38.8 (-40.9, -36.8; p<.0001) for the 40-64 group. This represents an immediate reduction of 3,835 newly billed glaucoma patients in the 20-39 group and 15,500 in the 40-64 group. In the policy unaffected 65+ group, the number of patients with a new glaucoma billing per 10,000 was stable after 2004 (+0.10, p=0.9).

The percentage of new glaucoma billings by ODs at major exams among all patients with a new glaucoma billing by ophthalmologists and ODs decreased immediately from 2004 to 2005: 11.0% (p<.0001) from 34.9% in 2004 for Ontarians aged 20-39, and 9.9% (p<.0001) from 32.5% for those aged 40-64. The 65+ group saw little change from 20.3% after 2004 (+0.5%, p=0.5).

Similar patterns were observed in Ontarians residing in rural vs urban areas and in the lowest vs the highest income quintiles.

Conclusion: Ontario's delisting of REEs was associated with significantly reduced optometric glaucoma diagnostic billings at major exams in the policy affected 20-64 groups, irrespective of socio-demographics. Further studies are required to determine if these reductions represent an increase in actual undetected glaucoma.

S.5: Umbrella review: Self-regulation in neurodevelopmental conditions—from conceptualization to measurement

Student: Iciar Iturmendi-Sabater, Supervisor: Meng-Chuan Lai

Background: Individuals with neurodevelopmental conditions (NDCs) such as autism, attention-deficit/hyperactivity disorder (ADHD), and intellectual disabilities (ID) often experience self-regulation difficulties (i.e., dysregulation). Although dysregulation appears transdiagnostic across NDCs, the current conceptualization and measurement are heterogeneous.

Purpose: This umbrella review aims to clarify how dysregulation is conceptualized and measured in NDCs.

Hypothesis: Despite variability in definitions, common patterns in dysregulation-related constructs and measurement tools will emerge across NDCs, reflecting shared underlying processes on top of condition-specific traits.

Methods: We searched Medline, PsycINFO, Embase, Web of Science–Core Collection, Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews. We included reviews that examined self-regulation in NDCs. We synthesized self-regulation definitions and related constructs via a content analysis, and quantified common use of self-regulation measurements. Risk of bias was assessed through the Joanna Briggs Institute checklist.

Results: From 18,821 citations, we included 35 narrative reviews, 2 scoping reviews, 9 systematic reviews, and 3 meta-analyses, covering autism (n=11), ADHD (n=24), ID (n=5), obsessive-compulsive disorder (n=2), and transdiagnostic studies (n=7). Self-regulation definitions varied considerably, but dysregulation emerged as a transdiagnostic phenomenon linked to several specific psychological constructs. Included reviews addressed its biology, developmental pathways, temporal courses, and interactions with the social contexts through co-regulation and adaptation. We identified 567 instances of self-regulation measures—primarily questionnaires (n=412)—with parents as the most frequent reporters (n=225). The most common measures were the Child Behavior Checklist, Aberrant Behavior Checklist, Behavior Rating Inventory of Executive Function, Difficulties in Emotion Regulation Scale, Conner's Rating Scale, and Emotion Regulation Checklist.

Conclusions: This umbrella review synthesizes the current conceptualization of self-regulation and presents a roadmap to operationalize self-regulation as measurable, non-modular, transdiagnostic processes across NDCs.

S.6: Machine learning algorithms to predicting heavy episodic drinking in the United States using survey data

Student: Laura Llamosas Falcon, Supervisor: Jurgen Rehm

Background: Heavy episodic drinking (HED) is a major public health concern but is often unreliably measured due to biases. While traditional methods like logistic regression can predict HED, machine learning algorithms (MLAs) have the potential to offer greater predictive accuracy and robustness.

Purpose and hypothesis: This study compares various MLAs to identify the best predictor of HED, using US survey data and focusing on five key features: average daily alcohol use, age, sex, socioeconomic status, and race and ethnicity. We will test the hypothesis that MLAs will outperform logistic regression in predicting HED.

Methods: Data from the 1997-2018 National Health Interview Survey was used. Logistic regression, naïve bayes, k-nearest neighbor, support vector machine, random forest, and XGBoost were trained and cross-validated. Performances were compared, and the SHapley Additive exPlanations method demonstrated the interpretability of the optimal model.

Results: The probability of correctly ranking a randomly selected HED instance higher than a non-HED instance ranged from 0.66 to 0.97, with XGBoost outperforming other models. Average daily alcohol use and age had the highest influence on the model's output.

Conclusions: The strong discriminative ability of our models shows that even a limited number of well-chosen features can yield robust predictions. This highlights the potential of MLAs for modeling health behaviors like HED, influenced by multiple interacting factors. Integrating our models into simulation frameworks can help model HED and test scenarios, leading to more effective policies. Future studies should incorporate objective sources for external validation and investigate systematic biases to improve predictive accuracy.

S.7: Impact of time-to-surgery on adverse outcomes for distal radius fractures: A population-based study

Student: Jonathan Persitz, Supervisor: David Urbach

Background and Purpose: The optimal timing for surgical fixation of distal radius fractures (DRF) remains a topic of debate, with previous studies reporting mixed findings. This study explores the relationship between surgical timing and postoperative adverse outcomes to determine the ideal window for intervention in acute DRF management.

Hypothesis: We hypothesize that surgical fixation of DRF performed more than 14 days after injury is associated with a higher rate of adverse outcomes compared to surgeries performed within 14 days.

Methods: This retrospective population-based study analyzed Ontario administrative health data from 2010 to 2020, including 13,389 adults who underwent surgical fixation for DRF. Wait time was analyzed as a continuous variable based on the duration between emergency department presentation and surgery. The primary outcome was composite complications occurring within 10 years of the index surgery, included infection, revision and hardware removal surgery. Secondary outcomes were post-operative infection within 1 month and revision surgery within 1 year. To address potential confounding by indication, we employed an instrumental variable analysis using institutional-level wait times. Time-to-event Cox multivariable models calculated hazard ratios (HRs) with 95% confidence intervals (CIs), adjusting for demographics, comorbidities, surgeon volume, type of fixation and hospital type (teaching vs. non-teaching).

Results: Surgeries performed between 6-20 days had a 13% lower risk of composite complications compared to those performed within the first two days (HR: 0.85, 95% CI: 0.73-0.98, P=0.03 for 6-9 days, HR: 0.78, 95% CI: 0.68-0.91, P=0.001 for 10-15 days and HR: 0.97, 95% CI: 0.66-0.95, P=0.01 for 16-20 days). Infection risk was also decreased by 38% for surgeries within 6-15 days (HR: 0.64, 95% CI: 0.45-0.91, P=0.01 for 6-9 days and HR: 0.59, 95% CI: 0.42-0.85, P=0.004 for 10-15 days). At the institutional level, patients in the 6-9 day and 10-15 day wait-time groups had a significantly lower risk of infection compared to those in the 1-5 day wait-time group (HR: 0.73, 95% CI: 0.55-0.96, P=0.02 and HR: 0.65, 95% CI: 0.47-0.89, P=0.007, respectively). Surgeries delayed beyond 25 days were associated with progressively worsening outcomes, though statistical significance was not reached (HR: 1.10, 95% CI: 0.81-1.49, P=0.55 for 26-30 days).

Conclusion: DRF surgery within 6–20 days was associated with the lowest risk of composite complications, with surgeries performed within 6–15 days offering the most comprehensive benefits, including the lowest risk of composite complications and infection. These findings highlight the importance of precise surgical timing, with 6–15 days representing the optimal window for minimizing postoperative complications.

S.8: Drinking outcomes and client satisfaction in an intensive virtual treatment program with remote abstinence monitoring for alcohol use disorder

Student: Ayla Sadeghi, Supervisor: Victor Tang, Matthew Sloan

Background: For many patients, it is difficult to access residential treatment for addiction due to financial and geographic barriers. Telemedicine-delivered interventions have been effective in the treatment of substance use disorders and could potentially be used to deliver care similar to residential treatment centers. We conducted a pilot study investigating the feasibility of a 4-week virtual intensive treatment program for alcohol use disorder (AUD) that aimed to offer similar care to a residential facility and used take-home breathalyzers equipped with facial recognition and data connectivity to monitor abstinence from alcohol. Here, we present preliminary data on client satisfaction and drinking outcomes from the program.

Methods: Forty individuals with moderate to severe AUD were enrolled in the program. The proportion of patients that completed treatment, client satisfaction (measured using the Client Satisfaction Questionnaire-8 [CSQ-8]) and drinking outcomes collected at baseline and following each week of treatment were assessed.

Results: Ninety percent of participants completed treatment. At the end of the treatment, the median CSQ-8 score was 30.0 (SD = 3.8) out of 32, indicating high treatment satisfaction. Binge drinking days (β = -3.21, 95% CI -4.12, -2.31, $p < 0.001$) and drinks per day (β = -4.43, 95% CI -5.69, -3.18, $p < 0.001$) decreased from baseline to end of treatment. Abstinent days per week increased over the course of treatment (β = 3.63, 95% CI 2.75, 4.50, $p < 0.001$).

Conclusion: These findings provide evidence supporting the feasibility of intensive virtual treatment with remote abstinence monitoring for AUD.

T: Population Health & Education

T.1: Towards automating adverse drug event systematic reviews

Student: Qanita Turabi, Supervisor: Christopher Parshuram, Frank Rudzicz

Background: Systematic reviews (SRs) are structured summaries of existing literature designed to answer specific research questions. SRs play a crucial role in research but are time- and resource-intensive. On average, an SR takes over 67 weeks and academic institutions spend more than $18.6 million annually to publish 132 SRs.

SRs focused on Adverse drug events (ADEs) are important as they help improve medication safety and can directly impact lives. ADEs – unintended harm from medications – account for 15% of hospital admissions in older adults and contribute to over 100,000 deaths annually. However, research has shown that better knowledge can reduce the occurrence of ADEs. Therefore, increasing the efficiency of ADE focused SRs is particularly important.

Additionally, machine learning and Large Language Models (LLMs) are transforming medicine by enhancing knowledge processing, making them valuable tools for supporting clinical decision-making. They also show promise in assisting with SRs. However, LLMs must be used in safe and controlled ways with proper understanding of their performance and implications.

Purpose: Develop an AI-based application to facilitate systematic reviews focused on ADEs

Hypotheses

H1. A tool specialised for ADE SRs can speed up the annotation process.

H2. Leveraging LLMs to provide guidance to human annotators can further speed up the annotation process without degrading the accuracy of human annotators.

H3. An LLM-based virtual annotator can be used to automate parts of the annotation process with accuracy equal to or higher than that of human annotators.

Methods: We developed a web-based tool to streamline ADE-focused systematic reviews. The tool automatically extracts key information relevant to ADEs, including drugs mentioned, MedDRA terms and MeSH headings from study data and presents it intuitively to annotators. The tool leverages Ollama, a platform for running LLMs, to process specialized prompts with study data to assist portions of the annotation process or potentially automate entire steps. This tool will be compared against Covidence, an established systematic review platform. Additionally, its performance will be evaluated with and without LLM-enabled features to assess the specific impact of LLM integration.

Results: To date, we have developed the annotation tool. Using an annotated dataset of 1,082 papers, we evaluated various open-source LLMs for classifying studies as relevant or not for an ADE SR. We found that BioGPT performed best, achieving 90.0% precision and 71.4% recall, while BioBERT had a lower precision at 75% but a higher recall at 85.7%.

Conclusions: We have successfully developed an annotation tool tailored for ADE-focused SRs and evaluated several LLMs for their ability to assist in parts of the SR process. Preliminary results suggest that BioGPT shows strong potential as the LLM to integrate into our tool. Our next steps will focus on having annotators use both our tool and Covidence on sets of papers to measure 1) the time-efficiency of our specialized tool and 2) the impact on accuracy of using LLM-based guidance and 3) whether LLMs can fully automate the inclusion/exclusion decision without compromising accuracy.

T.2: Placental pathology profiles in low-risk pregnancies with low circulating PLGF

Student: Sumaiya Ahmed, Supervisor: John Kingdom

Background: Placental dysfunction is a leading cause of obstetrical complications such as preeclampsia (PE), HELLP syndrome, fetal growth restriction (FGR), and fetal demise. These clinical syndromes can arise from underlying placental diseases such as maternal vascular malperfusion (MVM), fetal vascular malperfusion (FVM), villitis of unknown etiology (VUE) and other placental conditions contributing its dysfunction. Placental growth factor (PlGF) screening is a tool which can be used to identify pregnancies with underlying histopathological hallmarks of placental disorders.

Purpose and Hypothesis: This is a secondary analysis of a prospective cohort study conducted at a tertiary care center between 2020 to 2023. Pregnant people with singleton pregnancies underwent PlGF screening alongside routine gestational diabetes screening between 24 to 28 weeks' gestation. Those whose placentas were subsequently sent for pathological testing upon delivery were included.

Exposure: PlGF level less than 100 pg/mL at the time of gestational diabetes testing.

Outcomes and Measures: The primary outcome was incidence of features of various placental disease. Secondary outcomes included features of multiple placental diseases, low placental weight percentile, preterm birth, preeclampsia, and stillbirth.

Results: Among 1361 pregnancies analyzed, 79 (6%) pregnancies had PlGF level of less than 100 pg/mL. The low PlGF cohort had a median (IQR) age of 34 (31 to 39) years at the time of delivery, where there was 12 (15.2%) Caucasian individuals, 4 (5.1%) Black individuals, 4 (5.1%) Asian or South Asian individuals, 14 (17.7%) individuals who identified as other and 45 (57.0%) individuals with unknown race data. All placentas within the low PlGF cohort exhibited features of placental disease. Preterm birth accounted for 433 (31.8%) pregnancies in the overall cohort. Features of MVM were present among 555 (40.8%) placentas, with 412 (30.3%) exhibiting features of FVM and 412 (30.3%) bearing features of inflammatory lesions.

Conclusion and Relevance: These findings suggest preterm birth accounts for one third of the placenta's analyzed exhibiting signs of placental dysfunction. Due to the low-risk demographic of this cohort we expected to fewer pregnancies with low PlGF levels (<100 pg/mL). This is a preliminary, descriptive analysis of an ongoing project in which we hypothesize that low circulating PlGF will be liked to an increase in pathological features of placental diseases. Identifying pregnancies with underlying features of placental diseases using midpregnancy PlGF screening may be a strategic clinical tool which could be used to mitigate further obstetrical complications during pregnancy.

T.3: Exploring primary care and population health professionals' perspectives on AI-driven diabetes prediction and complication risk tools: Applications for point-of-care and population health planning

Student: Sameen Ali, Supervisor: Lorraine Lipscombe

Background: Type 2 diabetes (T2D) disproportionately affects marginalized populations due to social determinants of health (SDOH), such as income level, healthcare access, and food security. AI-driven predictive models integrating SDOH can identify high-risk populations, enabling early detection and targeted preventive care. These models can also support clinicians in prioritizing high-risk patients for intervention. Three AI models have been developed to enhance early detection, targeted intervention, and resource planning for diabetes care.

Purpose: This study aims to explore primary care and population health professionals' perspectives on AI-driven diabetes prediction tools, examining their implications for clinical decision-making and public health resource allocation.

Hypothesis: Healthcare providers' perspectives will reveal critical barriers and facilitators influencing the adoption of AI-driven diabetes prediction tools in both point-of-care and population health planning.

Methods: A qualitative study will be conducted using focus groups with primary care providers in Mississauga. A structured focus group guide will be developed based on the Theoretical Domains Framework (TDF) for point-of-care models and the Nonadoption, Abandonment, Scale-up, Spread, and Sustainability (NASSS) Framework for population-level models. Sessions will be recorded, transcribed, and analyzed thematically using NVivo.

Results: Preliminary qualitative analysis from stakeholder engagement has identified themes related to the adoption of AI-driven diabetes prediction tools. Healthcare providers expressed concerns regarding trustworthiness, interpretability, and equity, emphasizing the importance of AI models producing transparent, clinically relevant outputs rather than complex, opaque predictions. Concerns about scalability and ethical deployment were also raised, particularly regarding the integration of SDOH to ensure that predictive models do not exacerbate health disparities.

Additionally, early findings from focus groups and interviews with healthcare professionals in Peel Region indicate a strong interest in AI-driven tools for diabetes prediction, provided they are culturally tailored and co-designed with stakeholders to enhance feasibility and adoption. These initial insights will inform subsequent thematic analysis and the refinement of implementation strategies to support AI integration into clinical workflows.

Conclusions: Findings will contribute to understanding the feasibility, scalability, and acceptability of AI-driven diabetes prediction tools in healthcare settings. This study will provide recommendations for improving AI tool adoption and integration into primary care and population health frameworks.

T.4: Assessing the characteristics, houaing needs, and preferences for forensic patients designated ALC

Student: Vanessa Ip, Supervisor: Vicky Stergiopoulos, Alexander Simpson

Background: For individuals found Not Criminally Responsible on account of a Mental Disorder (NCRMD), appropriate housing is necessary for reducing recidivism and facilitating independent living. Forensic patients are at greater risk of housing vulnerability, homelessness, and substance-use. The literature on supportive housing for forensic populations is scant and appropriate housing is in short supply.

Purpose and Hypothesis: This thesis describes a multi-methods aiming to identify the characteristics of forensic patients designated ALC, their housing needs and preferences, and healthcare provider experiences in accessing and providing housing supports for this population.

Methods: This multi-methods study includes a clinical chart review of forensic patients designated alternate level of care (ALC), qualitative interviews with n=15 forensic patients awaiting for housing; and focus groups with CAMH clinicians (n=9).

Clinical chart data from the past 5 years (2018-2023) was extracted through a data pull of variables from clinical charts (I-CARE)(n=179). Demographic and clinical variables that were extracted include date of ALC designation, date of admission, sex, gender, age, racial group, sexual orientation, marital status, income, source of income, index offences, NCR/UST finding, psychiatric diagnoses, and clinical assessment and risk management scores. The most recent patients designated ALC (n=100) underwent manual extraction of specific variables related to their psychiatric diagnoses, substance use, criminal charges, problematic behaviour, and previous supportive housing through patients' updated ORB report and clinical charts.

Both patients and clinicians were recruited through convenience sampling, by speaking to CAMH physicians, forensic inpatient unit nursing staff, and allied health staff. Audio recordings were collected by a recorded WebEx meeting and securely stored on a CAMH-issued electronic device. All patient participants provided written informed consent prior to the demographic questionnaire and interview. Each interview lasted approximately 30 to 45 minutes. The research student, Vanessa Ip, asked questions discussing and probing about their housing history, and housing needs and preferences. Two focus groups, each lasting around 60-minutes, were conducted with two different forensic units at CAMH. To compensate participants for their time, they received a $30 gift card of their choice. A constructivist lens with qualitative description informed by stigmatized and marginalized populations was used to analyze the qualitative data. An iterative process was used for qualitative analysis and dissemination of results by referring back to the transcripts, coding, themes, and sub-themes. Descriptive statistics were calculated from the quantitative data using RStudio.

Results: Four qualitative themes emerged from the interviews and focus groups: (1) Awaiting Housing, (2) Complex Patient Treatment Experiences, (3) Navigating the Institutional Circuit, and (4) Perceived Health Needs and Housing Preferences. An additional two themes emerged solely from the focus groups: (1) barriers to community access and (2) recommendations to best support forensic patients designated ALC. The results provide context into the lived experiences of this population and inform the development of therapeutic programs and housing solutions for forensic patients.

T.5: Enabling surgical coaching through artificial intelligence: Enhancing mastery with tool-tissue interaction feedback

Student: Ziyad Khatab, Supervisor: Amin Madani

Background: The field of surgery demands a high level of precision and skill, and traditional training methods may fall short in adequately preparing surgeons for complex procedures. Traditional coaching is effective in improving surgical skills, but it is slow, inconsistent, and constrained by the limited time and availability of expert surgeons. AI and computer vision offer a way to revolutionize surgical education by providing objective, data-driven feedback to enhance skill development.

Purpose: Our research aims to develop an AI-driven computer vision platform for surgical training. Our existing model, GoNoGoNet, identifies safe ("Go") and unsafe ("No-Go") dissection zones in surgical videos. To enhance this, we propose integrating a Tool-Tissue Interaction (TTI) model that quantifies surgical performance, providing precise feedback on dissection safety and efficiency.

Hypothesis: We hypothesize that AI-based TTI analysis will enhance surgical training by offering quantifiable performance assessments. By integrating TTI with GoNoGoNet, we aim to create a system that helps surgeons refine their techniques and improve patient outcomes through objective feedback.

Methods: Using machine learning, we will develop a TTI detection model to analyze tool-tissue interactions in real time. This model will complement GoNoGoNet by providing a summary statistic, allowing surgeons to assess their performance based on validated AI analysis.

Results: The integrated system will generate a summary statistic offering: Objective feedback on dissection quality, standardized skill assessment for surgical trainees, guidance for training and performance improvement. This data-driven approach will ensure consistency in surgical education, improving precision and safety.

Conclusion: AI-driven feedback has the potential to transform surgical education by providing real-time, quantifiable performance assessments. Our integrated GoNoGoNet + TTI system will enhance training, standardize skill evaluation, and ultimately improve surgical outcomes.

T.6: Longitudinal predictors of mental health crisis service utilization in children and youth with neurodevelopmental disorders

Student: Sophia Lenz, Supervisor: Danielle Baribeau

Background: Children and youth with neurodevelopmental disorders (NDDs), such as autism or intellectual disability, are at greater risk of experiencing mental health/behavioural symptoms necessitating crisis service utilization. Despite this, the clinical, social, and environmental predictors of mental health crises in this population remain largely unknown.

Purpose and Hypothesis: This study aimed to identify predictors of mental health crisis service utilization in children and youth with NDDs. We hypothesized that social factors, including trauma and major life stressors, as well as financial strain, would emerge as significant predictors.

Methods: A retrospective chart review study was done to collect longitudinal demographic, clinical, social, and environmental data from the Holland Bloorview Kids Rehabilitation Hospital Psychopharmacology Clinic. This clinic provides psychotropic medication management to children and youth with NDDs that have high behavioural care needs. We then used cox proportional hazard regression models to determine how various clinical and environmental factors impacted the incidence rate of mental health/behavioural crises resulting in emergency service use (hospital, ER, police, crisis team) over time during clinical care.

Results: Charts from a total of 2994 visits across 389 unique psychopharmacology clinic patients were reviewed. Children were followed for a mean of 22-months (SD 18 months). During follow-up in clinic, 26.0% of patients experienced a mental health/behavioural crisis resulting in emergency/crisis service use. Multivariate cox proportional hazard models showed that financial strain (Hazard ratio (HR) = 1.87 (1.2 to 2.9, $p < 0.01$)) was associated with increased risk of mental health crisis service utilization during follow-up, while traumatic experiences (HR = 0.92 (0.4 to 2.4, $p = 0.86$)) and major life stressors (HR = 1.43 (0.8 to 2.6, $p = 0.23$)) were not.

Conclusion: Children and youth with NDDs are at high risk of experiencing mental health or behavioural crises. In our clinical cohort, financial strain significantly predicted incidence of mental health crisis service utilization. Future analyses should further investigate the relationship between traumatic experiences/major life stressors and mental health crises. These results may be influenced by sampling bias and therefore similar analyses should be carried out on a larger NDD sample with a broader range of behavioural care needs.

T.7: Barrier and facilitator beliefs about providing ongoing, integrated care for autistic children and their families: a qualitative exploration of community pediatricians' perspectives in Ontario

Student: Saebom Park, Supervisor: Melanie Penner

Background: Autistic children and their families report a high need for ongoing, integrated, and family-centered care to support their needs throughout their care journey. Community healthcare providers (HCPs) are uniquely positioned to fill this service gap due to their early and ongoing connections with families. However, many community HCPs do not feel equipped to provide this care. Project ECHO Autism (Extension for Community Healthcare Outcomes) is an evidence-based program that builds capacity for best-practice autism care in community settings, and offers an opportunity to educate and support community HCPs in providing ongoing integrated care. Understanding community HCPs' barrier and facilitator beliefs about providing ongoing integrated care can help to inform strategies to best support and empower community HCPs, and using a framework rooted in behaviour change such as the Theoretical Domains Framework (TDF) facilitates this process.

Purpose: Identify community pediatricians' barrier and facilitator beliefs about providing ongoing integrated autism care.

Methods: Eight general pediatricians (6 female; 2 male) practicing in seven health regions across Ontario participated in semi-structured focus groups over Zoom. Interview questions were guided by the TDF. Two coders first identified barriers and facilitators to providing ongoing integrated care. Barriers and facilitators were then mapped onto one of the 14 domains of the TDF. For each barrier and facilitator, a belief statement was generated to convey the central underlying belief based on participant responses. Coding and belief statements were checked and discussed between two coders.

Results: We identified a wide range of barrier and facilitator beliefs about providing ongoing integrated care. Several barriers and facilitators were identified in the *Knowledge*, *Social and Professional Role, Beliefs about Consequences*, and *Environmental Context and Influences* domains of the TDF. Some notable barrier beliefs were related to a lack of in-depth knowledge about the service landscape, challenges in setting boundaries and defining responsibilities in community-based practice, the lack of guidance in service navigation, and the confusing and constantly changing nature of the service system. Some beliefs that facilitate the provision of ongoing integrated care included how ECHO Autism provides a source of knowledge for resources and tools for managing co-occurring conditions with autism, understanding one's role in navigating and coordinating services for families, as well as the belief that ongoing care is valuable in a family's care journey.

Conclusion: Our findings suggest there are many possible barrier and facilitator beliefs to address in supporting community HCPs in their ability and confidence to provide ongoing integrated autism care. For instance, a comprehensive resource with up-to-date information about services in a community could be valuable in helping community HCPs navigate the confusing and changing service landscape. With these results, our team will consult with broader knowledge users including autistic advocates and families to develop toolkits supporting ongoing autism care.