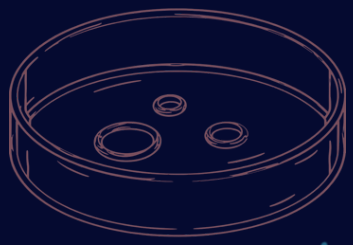
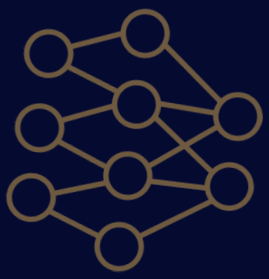
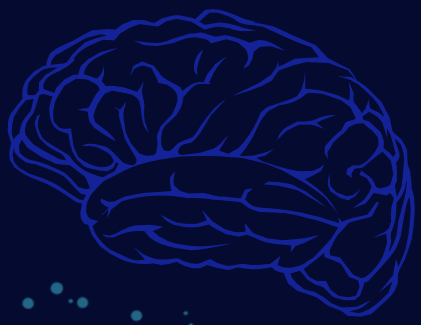


2026 MBP Symposium

ABSTRACT BOOKLET

Medical Biophysics
UNIVERSITY OF TORONTO

JLM
James Lepock Memorial Committee

MBP Symposium

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Upper Year Seminar #1

Pediatric pan-cancer characterization of transposable elements and their modulation by germline *TP53* variants

Brianne Laverty (Supervisor: David Malkin)

Transposable elements (TEs) are dynamic repetitive genomic regions that are epigenetically silenced and can become reactivated under stress, driving genomic instability and aberrant gene regulation. Although TE activation is a well-recognized feature of embryonic development and adult cancers, their role in pediatric malignancies is poorly understood. Approximately 15-18% of pediatric cancers arise in the context of hereditary cancer predisposition syndromes, such as Li-Fraumeni Syndrome, caused by germline variants in *TP53* (g*TP53*). *TP53* binds LINE1 elements to suppress their transcription, and adult tumors with somatic *TP53* mutations exhibit elevated TE activity. These findings suggest that g*TP53* variants may disrupt TE regulation, predisposing tissues to malignant transformation. To investigate this, we characterized the germline and tumour TE landscape across a pediatric pan-cancer cohort and evaluated the impact of g*TP53* variants.
TEs were identified in 753 germline and 410 tumour samples from pediatric cancer patients. Germline ALU, LINE1, SVA elements were called using MELT, xTEA, and INSurVeyor, while tumor LINE1 elements were called with xTEA and TotalReCall. We excluded 95% of germline TEs classified as common (>3% of gnomAD or our cancer-free cohort [n=298]).

Pediatric tumors exhibit a quiet LINE1 landscape, with only 30% of tumors harbouring at least one insertion, significantly fewer than adult tumors ($p<0.05$). Colorectal cancers contained significantly more LINE1s, consistent with patterns observed in adult-onset malignancies. Tumors containing $\geqslant$1 insertion were associated with poorer survival ($p<0.1$) and transcriptomic pathway analysis revealed enrichment of DNA replication and cell-cycle progression pathways ($q<0.05$). In contrast, tumors with low LINE1 burden were enriched for immune response pathways ($q<0.05$), recapitulating transcriptomic patterns observed in adult cancers. Interestingly, low LINE1 burden tumors from g*TP53* carriers were not enriched for immune response pathways and instead were associated with an increase in RNA processing and ribosomal biogenesis, demonstrating alternative TE suppression mechanisms in g*TP53* carriers.

We observed no difference in germline or tumor TE burden between g*TP53* carriers and non-carriers, prompting us to examine insertion-site patterns. Motivated by prior findings of global germline methylation differences in g*TP53* carriers, we evaluated if g*TP53* variants alter germline insertion location by training a regularized logistic regression model on TE distribution. The model predicted g*TP53* status with an AUPRC of 0.71 (95% CI, 0.59-0.85), suggesting gTP53 variants influence germline insertion positioning. The model maintained strong performance with 50% of the features (AUPRC=0.64), demonstrating positioning effects are globally distributed rather than driven by a small subset of windows. We will use AlphaGenome to hypothesize the effect of this dysregulated germline TE landscape in g*TP53* carriers.
This is the first characterization of pediatric pan-cancer transposable elements in germline and tumor genomes. This establishes germline and tumor TE dysregulation as a feature of g*TP53*-associated cancer and will inform future studies on early cancer development and treatment for g*TP53* carriers.

Upper Year Seminar #2

Determining Depth-Specific Effective Connectivity from Dynamic Causal Modelling using High-Resolution BOLD fMRI data

Yuexin Xi (Supervisor: Kamil Uludag)

Introduction. The blood oxygenation level-dependent (BOLD) signal is widely used to measure brain activity in functional magnetic resonance imaging (fMRI). Because the BOLD signal arises from complex physiological processes, accurate interpretation requires biophysical models incorporating neural and vascular dynamics. Building on such models, dynamic causal modelling (DCM) provides a framework to infer causal influence (i.e. effective connectivity) between brain regions from task-related fMRI. Characterizing these interactions is critical for understanding cognitive processes and their disruption in neurological and psychiatric disorders. Advances in ultra-high-field MRI now enable submillimeter-resolution fMRI, allowing investigation of cortical depth-specific interactions. However, existing approaches rely on correlations between BOLD signals, and no established fMRI model exists for estimating depth-specific effective connectivity. We therefore aim to develop an invertible, physiologically informed laminar fMRI model and evaluate the capacity of high-resolution fMRI in reflecting brain activity and effective connectivity.

Methods. The model is based on an existing laminar framework, with depth-specific components for neuronal activity, neurovascular coupling, hemodynamics and signal observation. In this project, the concept of canonical microcircuit (CMC) is introduced into the neuronal model so that each region comprises three neuronal depths (supra-, infragranular layers and the granular layer 4). Three alternative models were implemented: an independent model, a CMC feedforward model, and a CMC feedback model. To assess model invertibility, simulation analyses were conducted to examine whether the microcircuit models can be distinguished based on model evidence (defined as the ratio of model accuracy to complexity) during inversion of simulated data. Four sets of time series were generated: from the CMC feedforward model, input was applied to the 1) middle layer, and from the CMC feedback model, input was applied to the 2) superficial layer, 3) deep layer and 4) both layers. Each set of synthetic time series was then inverted using all three neuronal models with identical priors.

Results. Simulations 1, 2 and 4 produced profiles exhibiting an overall increase in signal change towards the cerebrospinal fluid (CSF) boundary, whereas simulation 3 exhibited an overall decrease towards the CSF boundary. Model comparison demonstrated that the feedforward model showed the highest evidence for feedforward-generated data (simulation 1) and the feedback model showed the highest evidence for feedback-generated data (simulation 2, 3 and 4).

Discussion. The BOLD profiles in simulation 1, 2 and 4 align with patterns reported in empirical studies, supporting the physiological plausibility of the proposed microcircuit models. The microcircuit models were successfully distinguished through model inversion in all simulations. Notably, the CMC models yielded evidence higher than the independent model, demonstrating an improved accuracy without introducing unnecessary complexity. Future work will evaluate model invertibility using empirical data.

Conclusion. This work presents the first invertible laminar BOLD-fMRI model for investigating depth-specific effective connectivity. This framework enables more accurate interpretation of depth-specific interactions from fMRI beyond correlation-based approaches, offering a new opportunity to study brain region interactions and their disruptions in neurological disorders at the mesoscopic level.

Upper Year Seminar #3

Evaluating PARP Inhibitors for Primary Breast Cancer Prevention

Olivia Drummond Guy (Supervisor: Rama Khokha)

High-risk individuals such as those with hereditary BRCA1 mutations commonly develop triple-negative breast cancers (TNBC). To reduce their lifetime risk, patients are left with limited options for breast cancer prevention, such as invasive prophylactic mastectomies or selective estrogen receptor modulators that do not reduce the risk of hormone receptor-negative breast cancers. The lack of more precise prevention methods indicates an urgent need for strategies that specifically target cancer-prone cells in the breast.

Stem and progenitor cell populations residing in the basal and luminal lineages maintain the mammary epithelium. In the high-risk breast, stem and luminal progenitor cells are thought to give rise to aggressive breast cancer subtypes such as TNBC. Therefore, novel chemo-preventative strategies must target these putative cell-of-origin populations in breast cancer. Currently, poly (ADP-ribose) polymerase (PARP) inhibitors (PARPi) are harnessed in the clinic to treat hormone receptor negative breast cancers with hereditary BRCA1/2 mutations. PARPi may be clinically repurposed as a targeted chemoprevention agent to exploit lineage-dependent PARPi vulnerabilities to prevent the onset of tumor development. Research exploring mammary characteristics is an essential step towards identifying lineage-specific differences to target with prevention therapies. Studies have revealed a lineage-specific sensitivity to PARPi by assessing progenitor capacity using colony forming cell assays treated with PARPi of human and mouse luminal and basal progenitors.

The Khokha lab has established mouse models of adult mammary development and ex vivo human models including patient-derived mammary organoids (PDMOs) reflecting the high-risk breast and mammary lineage-specificity for the successive evaluation of drug efficacy. I hypothesize that PARPi treatment will selectively target mammary progenitor cells with BRCA1 mutations. I will assess the effects of 3rd generation PARPi olaparib and next-generation PARPi saruparib treatment on high-risk mammary epithelium.

In this work, I will assess effects of PARPi on in vivo mammary mammopoiesis using BRCA1 mutant mice. Using our standardized method to test the effect of inhibitors on hormone-triggered mammopoiesis, I will establish PARPi dosing regimen, efficacy and toxicity. I will perform mammary gland wholemounts to quantify ductal side branching and alveologenesis and conduct fluorescence-activated cell sorting to quantify progenitor subset proportions and obtain cells to perform colony forming assays for progenitor cell activity.

I will further investigate molecular mechanisms of PARPi using ex vivo models of mammary progenitors, specifically human PDMOs. I will determine the capacity of PARPi to i) inhibit progenitor cell growth/proliferation and differentiation, ii) reduce viability of PDMOs, iii) alter PDMO organization (bilayer and branching), and iv) impact expression of specific proteins/lineage markers.

High-risk individuals lack personalized risk management. By leveraging mouse and human models of the high-risk breast, I will determine the efficacy and safety of PARPi to target mammary progenitors. This work will generate a molecular-guided rationale for preclinical chemoprevention studies to personalize risk management of high-risk germline mutation carriers.

Lower Year Seminar #1

Development of a Multi-Modal Deep Learning Pipeline for Automatic Segmentation of Clinical Targets in MRI-Guided HDR Brachytherapy

Soroush Ghomashchi (Supervisor: Alexandra Rink)

Introduction. High-Dose-Rate Brachytherapy (HDR-BT) is a critical part of cervical cancer treatments, with MRI-guidance serving as the gold standard for defining the Gross Tumor Volume (GTV) and Clinical Target Volumes (HR-CTV, IR-CTV). While MRI offers superior soft-tissue contrast, manual segmentation remains time-intensive. Existing automated approaches are predominantly CT-based1, and the only proposed fusion strategy lacks rigorous validation against baseline models. This study evaluates the efficacy of a 3D Deep Learning (DL) framework for MRI-based segmentation, specifically comparing the performance of single-view models versus multi-view ensemble architectures to determine the optimal strategy for clinical workflow efficiency and geometric accuracy.

Methods. The study cohort includes T2-weighted MRI planning scans from 70 patients (190 total fractions) with cervical cancer (FIGO: IB – IIIC2). Ground truth contours were manually delineated and reviewed by radiation oncologists. A self-configuring 3D U-Net (nnU-Net) was utilized to establish a single-view axial baseline. To assess the value of contextual information from orthogonal planes, separate models were trained on coronal and sagittal views and integrated into a multi-view ensemble using late fusion strategies (Hard Voting vs. Soft Averaging). Performance was evaluated using volumetric Dice Similarity Coefficient (DSC), surface DSC, and Hausdorff Distance (HD95). Clinical utility was assessed using Added Path Length (APL), quantifying the correction burden on clinicians.

Results. The single-view axial model demonstrated superior or equivalent performance to multi-view fusion strategies across all targets. For the challenging GTV, the axial model achieved a DSC of 0.54 ± 0.23 and an HD95 of 7.07 ± 5.18 mm, significantly outperforming both Hard (DSC: 0.49 ± 0.23 ($p = 0.01$), HD95: 7.09 ± 4.58 mm) and Soft (DSC: 0.50 ± 0.23 ($p = 0.02$), HD95: 7.11 ± 4.59 mm) fusion ensembles. Crucially, the axial model exhibited a significantly higher sensitivity compared to fusion methods ($p < 0.01$). The lower quantitative performance for GTV compared to other targets is attributed to the high surface-area-to-volume ratio of small targets. For larger targets, the axial model achieved high performance (HR-CTV DSC: 0.83 ± 0.05; IR-CTV DSC: 0.84 ± 0.05), with no statistically significant improvement observed from multi-view fusion ($p > 0.05$). In terms of clinical efficiency, the single-view axial model yielded significantly lower correction burden (APL) for GTV (6.53 ± 2.70 cm) compared to the Hard fusion ensemble (7.11 ± 2.83, $p = 0.01$).

Conclusion. This study demonstrates that a well-optimized single-view 3D axial architecture provides robust segmentation for MRI-guided HDR brachytherapy, outperforming complex multi-view ensembles. Future work will focus on addressing GTV class imbalance through generalized Dice loss, oversampling, cascade training, and integration of additional metrics. We will also compare this baseline model against other state-of-the-art DL architectures to further benchmark segmentation performance.

Lower Year Seminar #2

Diffusion-Based Generation of Synthetic Whole-Slide Images from Methylation Profiling

Sean D'Mello (Supervisor: Sushant Kumar)

Introduction. Machine learning models trained on both methylation sequencing data and whole-slide image (WSI) datasets have shown increased performance in cancer detection and prognosis compared to uni-modularmodels. However, the volume of available multi-modal datasets with both methylation sequencing and WSI is limited and greatly surpassed by the volume of uni-modal datasets. The use of synthetic data-artificial data generated by advanced deep learning models - addresses this limitation by increasing the volume of available training data, thereby improving model performance, especially for under-represented classes. We hypothesize that training machine learning models using both real WSIs and matched methylation data, supplemented with additional synthetic WSIs generated from methylation profiles, will improve model performance compared to training on real WSIs and methylation sequencing data alone.

Methods. To generate the WSIs from a methylation sequencing profile, a diffusion-based pipeline will be used. First, a beta variational autoencoder will be trained to generate a low-dimensional latent embedding for each methylation profile. Next, a diffusion model will be conditioned with the embedding from the beta variational autoencoder and trained to generate the corresponding WSI image. A second diffusion model will be trained and applied to increase tile resolution. To assess model performance, Frechet Inception Distance, Kernel Inception Distance, and Inception Score will be assessed. Additionally cell types will be classified using HoverNet, and cell distributions will be compared between real and synthetic patches. Synthetic data will be generated by conditioning the model with existing methylation sequencing datasets without corresponding WSIs, and through systematic perturbation of TCGA and CPTAC methylation sequencing datasets. To assess the utility of the synthetically generated WSIs, convolutional neural networks will be trained for tasks such as paediatric glioma prognosis prediction and microsatellite instability status prediction in colorectal cancer, comparing performance between a model trained solely with real WSIs and matched methylation data versus with real and synthetic data. The model will be trained using all available samples with both methylation sequencing and WSI in the TCGA dataset (n=5175). Model performance will be assessed using the CPTAC cohort (n=1641).

Expected Results. We expect to see improved performance in the machine learning models that use synthetic data. Additionally, we expect that classes with less real data in the training set will see a proportionally higher increase in accuracy due to higher class representation.

Conclusion and Significance. Overall, this study addresses a fundamental limitation in multimodal cancer modeling: the limited availability of datasets containing both methylation sequencing and whole-slide imaging. Through the generation of synthetic WSIs from methylation profiles, we propose a scalable strategy to augment existing multimodal datasets without the need for additional histopathological acquisition, enabling improved performance of models in computational pathology. Furthermore, the generative pipeline and resulting synthetic dataset will be made publicly available.

Lower Year Seminar #3

Energy-efficiency of pulsed transcranial and intranasal photobiomodulation in modulating brain rhythms.

Alicia A. Mathew (Supervisor: Jean Chen)

Introduction. Transcranial and intranasal photobiomodulation (tPBM; iPBM) are neuromodulation approaches that non-invasively deliver near-infrared (NIR) light to the brain to enhance neural activity. Both approaches act primarily via the photoexcitation of mitochondrial chromophores, up-regulating oxidative metabolism and ATP synthesis, but they use distinct optical entry routes. Prior work has demonstrated tPBM's effects on cortical oscillations, measured through electroencephalography (EEG), but it remains unknown whether iPBM can achieve equivalent neuromodulation and how efficiently the brain converts the delivered optical energy (dose) into measurable electrophysiological change. This work uses a dose-normalized metric to quantify efficiency as the percent-change in EEG power per J/cm^2 delivered, enabling meaningful comparison across delivery routes despite their markedly different irradiances. Methods. Healthy young adults (N=46; 20-32 years; 24M/22F) were randomly assigned to one of three protocols, each comprising eight EEG-PBM recordings spanning two wavelengths (808/1064 nm), two pulsation frequencies (10/40 Hz), and three irradiances. NIR light was delivered via MDL-III lasers through a custom headpiece (tPBM) or nosepiece (iPBM), both targeting the right prefrontal cortex. MR thermometry and participant self-reports confirmed no intracranial heating. Parameters were remotely controlled, keeping participants blinded to protocol, delivery method, and timing. Participants watched naturalistic videos throughout to minimize drowsiness and stabilize brain state. Each recording followed a PRE-DURING-POST block design (4 minutes each), with the PRE period serving as a within-subject baseline. EEG was recorded with a 256-channel HydroCel Geodesic Sensor Net. Preprocessing included high-pass filtering (1 Hz), resampling (125 Hz), automated channel rejection, and Independent Component Analysis to remove eye movements, muscle artifacts, and line noise. Power spectral density was estimated using Welch's method, and band-limited absolute power (delta, theta, alpha, beta, low gamma) was expressed as the percent-change from the mean of the PRE period. This was then averaged across all electrodes within the latter half of the DURING (Min 6-8) and POST (Min 10-12) windows. Efficiency was calculated from this mean percent-change divided by the energy delivered (J/cm^2), computed from irradiance, stimulation duration, and the 50% duty cycle of pulsed delivery. Two-sample t-tests statistically compared efficiency across irradiances with Benjamini-Hochberg false discovery rate (FDR) correction ($q<0.05$).

Results. Across all conditions, iPBM was at least an order of magnitude more efficient than tPBM. For tPBM, the highest irradiance (200 mW/cm^2) was generally least efficient, consistent with a biphasic dose-response, with efficiency peaking at 100 mW/cm^2 in lower-frequency bands and 150 mW/cm2 in beta/gamma. For iPBM, lower irradiances (5-7 mW/cm^2) consistently outperformed 9 mW/cm^2 across most bands and both wavelengths.

Discussion. The large efficiency gap between modalities likely reflects the anatomical advantage of the intranasal route, where NIR light traverses the thin cribriform plate rather than thick cranial bone, minimizing optical attenuation. Wavelength influenced the contrast between irradiance levels but did not alter qualitative efficiency patterns.

Conlusion. These findings position iPBM as a portable, convenient, and more energy-efficient modality for neuromodulation, especially relevant in clinical populations where PBM is being explored for stroke, depression, and neurodegeneration

Poster #1

Rapid treatment recommendations from AI-inspected blood smears in acute myeloid leukemia

Yuxi Yang (Supervisor: Gregory Schwartz)

Acute myeloid leukemia (AML) is an aggressive blood cancer in which delays in treatment initiation can rapidly lead to life-threatening outcomes. Current international genetic risk classification guideline stratifies AML patients at diagnosis into favorable, intermediate, and adverse risk groups based on their molecular landscape and cytogenetic analysis. These risk groups are associated with distinct survival outcomes and guide therapeutic decision-making. However, formulating an optimal treatment plan relies heavily on time-consuming molecular profiling workflows and may delay treatment initiation at diagnosis. As a result, there is a critical need for methods that can rapidly predict AML patient survival risk to inform treatment strategies at the time of diagnosis. Clinicians routinely collect peripheral blood smears from patients with AML during diagnostic procedure and digitize them into whole-slide images (WSIs). Recent advances in deep learning can now extract clinically relevant features from histopathological WSIs to predict survival and treatment response in solid tumors. Preliminary work from our lab demonstrates that associations between cellular morphology and mutations with known relevance to AML prognosis. Despite these advances, hematologic malignancies such as AML have not yet benefited from AI-based prognostic models that integrate cellular imaging with clinical data. To address this gap, this project aims to develop a deep learning framework that delivers rapid treatment recommendations using peripheral blood smears and clinical variables. I hypothesize that the cellular morphology within a patient with AML at diagnosis is predictive of optimal treatment. I will first develop a deep learning framework that integrates morphological features derived from peripheral blood smears with relevant clinical covariates to provide treatment recommendations. Then apply this model to a retrospective cohort of 500 AML patients with WSIs of peripheral blood smears and associated clinical data, balanced across disease risk groups, sex, age, and treatment strategies. I will assess model performance on a held-out evaluation set and further identify new morphologies that are most informative for AML patient outcome using explainable AI approaches. By complementing the traditional diagnostic procedure, this work has the potential to uncover previously unrecognized prognostic cellular phenotypes and significantly accelerate treatment planning at diagnosis. Ultimately, this model leads to more timely initiation of targeted therapies and improve clinical outcomes of AML by patient-specific biomarkers.

Poster #2

Investigating the structural mechanism of pharmacological PINK1 inhibition in acute myeloid leukemia

Elise Quadri (Supervisor: Steven Chan)

Acute myeloid leukemia (AML) is an aggressive hematological cancer that causes death in over 1000 Canadians annually. Although there exist effective therapeutic regimens to treat AML, relapse rates of up to 80% indicate sustained poor prognoses for this malignancy. This can be attributed to the inability of such treatments to eradicate leukemic stem cells (LSCs), whose long-term self-renewal capacities allow for their persistence and differentiation to re-establish malignant proliferation during hematopoiesis. Thus, there exists a need to develop therapies that effectively target and eliminate this cell subpopulation. One promising therapeutic target against LSCs is PTEN-induced kinase 1 (PINK1); a serine-threonine kinase responsible for inducing mitophagy following the detection of damaged mitochondria. Recent work from Dr. Steven Chan's laboratory has shown that knockdown of PINK1 expression induces LSC senescence by causing an accumulation of damaged mitochondria, stimulating integrated stress responses, and arresting cell cycle progression (unpublished). The dependence of LSCs on PINK1-induced mitophagy reflects the potential for pharmacological inhibition to effectively target this vulnerability with minimal off-target effects. One molecule, compound X, has been shown to strongly inhibit PINK1 and induce LSC senescence in vitro, while reducing leukemic burden with minimal toxicity in vivo. However, the exact mechanism by which this molecule inhibits PINK1 remains unclear. To characterize the structural basis of PINK1 inhibition by compound X, I will be employing cryo-electron microscopy to visualize recombinantly expressed and purified PINK1 in complex with this small molecule of interest. This will allow for the identification of key compound-residueinteractions that drive the inhibition of PINK1 activity, which will be further supported by functional evidence provided by interaction and kinase activity assays in the presence and absence of the inhibitor. The results from this study will facilitate further optimization of the design of potent PINK1 inhibitor compounds that can target the elimination of LSCs and ultimately attenuate the risk of AML progression and relapse mechanisms that are dependent on PINK1-meditated mitochondrial homeostasis.

Poster #3

Investigating Early Microglial Responses to Amyloid-β and Tau in Neuroimmune Organoid Models of Alzheimer's Disease

Elizabeth Wilson (Supervisor: Liliana Attisano)

Alzheimer's disease (AD) is a complex, progressive, neurodegenerative disease that leads to cognitive decline and is the most common cause of dementia. The accumulation of amyloid-β (Aβ) and tau, along with neuroinflammation and neuronal cell death, are hallmarks of the progression of the disease. In the past, animal models and 2D neuronal cell cultures have been the primary models used to study the pathology of AD. However, these models do not sufficiently recapitulate the complexity of the structure and cellular diversity of the human brain. Therefore, there is a need for more physiologically relevant models of human neural tissue to more accurately reconstruct the progression of neurodegenerative diseases. In particular, three-dimensional (3D) cerebral organoids (COs) derived from human induced pluripotent stem cells (iPSCs) provide a more functionally representative model to help probe how cell-cell interactions interplay in neurodegenerative disease. The multicellular composition of CO models is key for capturing the complex cellular interactions underlying neurodegeneration, but the lack of immune components in many neuronal models limits our ability to study neuroimmune interactions in AD. As the resident immune cells of the brain, microglia play a central role in AD pathogenesis, and are increasingly recognized as central regulators of Aβ clearance and inflammatory signalling. However, the precise role of microglia in the early stages of AD remains incompletely understood. To address this gap, we are developing a human iPSC-derived neuroimmune CO model to investigate early microglial responses to Aβ and tau accumulation in a human genetic context. We hypothesize that human iPSC-derived microglia incorporated into 3D COs will exhibit in vivo-like functional responses to early Aβ and tau accumulation, with wild-type and disease-associated microglia showing distinct phagocytic and inflammatory profiles. Human iPSCs will be differentiated into microglial precursors and matured into microglia in CO co-cultures. Lineage specification and microglial identity will be confirmed by immunofluorescence and qPCR. Microglial integration and functional responses to Aβ and tau will be assessed by phagocytosis and cytokine expression across isogenic control and disease lines. This model aims to demonstrate successful maturation and integration of iPSC-derived microglia within COs and recapitulate in vivo-like functional phenotypes. Microglia are expected to show functional responses to early Aβ and tau accumulation, with disease-associated microglia exhibiting distinct phagocytic and inflammatory profiles compared to controls. Observing these differences will provide insight into early microglial contributions to AD pathology. Overall, this project aims to establish a neuroimmune organoid platform for studying microglia-mediated responses in a human genetic context, with potential applications to other neurodegenerative disease models.

Poster #4

Modelling Drug Tolerance Development in Biliary Tract Cancer through Cellular Movement across Spatial Compartments

Ho Seok Lee (Supervisor: Gregory Schwartz)

Introduction. The five-year survival rate of biliary tract cancer (BTC) is as low as 9% in Canada. Despite the wide arsenal of treatments in place, ranging from systemic to locoregional, the vast majority of these therapies fail to consistently eradicate BTC, with recurrence rates as high as 75% within the first two years, demanding new approaches to investigate and fight BTC resistance. The current comprehensive model of drug resistance considers a complex interplay of epigenetic and genetic mutations, tumour microenvironment (TME) modulation, and phenotypic adaptation. While leveraging the TME is becoming an increasingly promising avenue for detecting new targets, few have considered the mechanical nuances behind such a crowded, dense environment. Recent evidence has demonstrated that physical factors such as cellular membrane pressures and heterogenous drug concentration enables invasive phenotypic behaviour and allow cellular communities to migrate, escape, and survive within the tumour. These findings suggest a broad range of mechanistic intra-tumour variables present in resistance evolution must be considered to overcome resistance in BTC. The overall goal of the project is to interrogate the evolution of resistance in BTC from a biomechanical perspective and detect potential targets for combination therapies. I hypothesize that physical cellular interactions, in particular the potential to migrate, and their corresponding transcriptomic changes predict additional molecular characteristics of the drug-tolerant TME of BTC.

Methods. Using spatial transcriptomics, a sequencing technology for tissue samples capturing both gene expression and physical positional context of single-cells, inter-cellular membrane tensor forces will be inferred from cell geometries. A unique spatial dataset relating changes in cellular pressure to transcriptomic changes in vitro will be used to translate the biomechanical domain to the transcriptomic, with a transformer model for gene-regulatory network (GRN) inference accounting for variable pressure. Using an active vertex model (AVM) to represent the cell geometries, the model will simulate the changes in cellular forces of the tissue over time, and, in conjunction with the transformer model, will infer the resulting transcriptomic changes. We will have access to a cohort of patient-derived xenograft (PDX) treatment-naive and drug-tolerant BTC spatial transcriptomic samples. Tissues in the drug-tolerant state will reveal the range of BTC-specific molecular strategies used to persist drug-exposure. Through the differential statistical analyses, cellular populations with higher potential for movement will be investigated for these same strategies related to possible drug-tolerant behaviour. Concurrently, we will elucidate not only single-cell phenotypic and genotypic characteristics, but also spatially-localized epigenetic characteristics, associated with intra-tumour cellular movement of drug-tolerant persister cells.

Results. The project is still in its preliminary stage, and no relevant results have been produced.

Conclusion. Through a variety new biomechanical dimensions that have not been considered in the context of drug resistance in BTC, we hope to find new depths to the behaviour of drug-tolerant persister cells in the tumour microenvironment. Leveraging the understanding gained from the AVM simulation and GRN transformer, we hope to find novel clinical targets and possible combination therapies to overcome BTC resistance.

Poster #7

Risk Monitoring for Women at High Risk of Breast Cancer Using Plasma Metabolomic and Lipidomic Signatures

Linghao Song (Supervisor: Rama Khokha)

Introduction. The inherited heterozygous pathogenic germline mutations, such as BRCA1/2, can lead to deficient DNA damage repair in carriers' breast epithelial cells and increase lifetime breast cancer risk >60%. Current screening methods, such as mammography and MRI, rely on detecting tumor mass and early lesions, including DCIS. However, non-invasive monitoring of early malignant alternations in the breast epithelium remains challenging. Menstrual remodeling of the breast involves proliferation, differentiation and apoptosis of breast epithelial cells, creating an opportunity for the release of breast-derived proteins and metabolites into the bloodstream. This biology supports the use of blood as a potential more accessible of breast cancer prevention option for healthy high-risk mutation carriers, complementing conventional screening methods. Combining proteomics and lipidomics may reveal risk-group-specific molecular signatures. Previous studies show that breast epithelial stem cells develop into different breast cancer subtypes base on their lineages and mutation acquired. For example, luminal progenitors (LP) are the purported cell-of-origin for BRCA1-mutant breast cancers. Metabolic programs, including post-transcriptional regulatory responses under replicative stress, are retained in tumor subtypes and their corresponding cells-of-origin. Identifying unique protein and metabolic signatures of the mammary stem cell population will support the development of breast-specific signature for early detection. I hypothesize that parallel proteomic and metabolomic interrogation of breast epithelial cells and plasma, will reveal early indicators of breast cancer risk.

Methods. To achieve this objective, we will 1. Identify risk-associated markers and pathways leveraging UK Biobank (UKB) plasma multi-OMICs and clinical history data. 2. Perform proteomics and metabolomics on menstrual cycle staged plasma samples from high-risk germline mutation carriers. 3. Associate plasma-based markers from UKB and breast breast-derived markers by co-expression profiling and pathway mapping.

Results. We performed differential gene expression analysis on proteomic data from BRCA germline variant carriers and non-high-risk germline variant carriers. Principal component analysis and K-means clustering by cell type, whereas gene-wise correlation analysis revealed genotype-associated structure. These gene clusters were consistent with the average fold changes observed between genotype subgroups and sample genotype annotations.

Discussion. The PCA and gene-wise correlation results suggest that both cell lineage and genotype-associated differences can be investigated through expression profiles and co-expression patterns. This analytical framework may also be extended to future multi-omics studies.

Conclusion. The comprehensive, matched multi-OMICS and clinical data in UKB will expand our understanding of molecular changes in high breast cancer risk mutation carriers. Integration of breast-derived signatures and plasma-based biomarkers supports the discovery of plasma biomarkers, reflects breast tumour progression, and leads to a more accessible and sensitive screening for healthy high-risk breast cancer populations.

Poster #9

Assay and structural analysis of mycobacterial EtfD as a target for fast-acting tuberculosis therapeutics

James Wang (Supervisor: John Rubinstein)

Introduction. Tuberculosis claims more than a million lives each year. Further, Mycobacterium tuberculosis (Mtb), the pathogen that causes TB, is increasingly resistant to existing drug treatments, threatening efforts to control the disease. Mtb reliance on metabolism of host-derived lipds during infection has been identified as a point of vulnerability that could be targeted to shorten TB treatment, making it more effective and reducing development of drug resistance.The Mtb protein EtfD links lipid metabolism to the bacterium's generation of chemical energy, and is a particularly attractive target because it is not homologous with the equivalent protein in humans. Furthermore, Mtb with EtfD knocked out is unable to survive in a mouse model of TB, and cannot grow on medium containing fatty acids. Refinement of an activity assay for EtfD will enables high-throughout screening of potential inhibitor compounds. This assay, in conjunction with electron cryomicroscopy (cryo-EM) structural analysis of EtfD in complex with inhibitors and the cytoplasmic electron transfer flavoprotein (ETF), will accelerate drug discovery for effective anti-TB therapeutics.

Methods. Mtb proteins will be expressed and harvested from the non-pathogenic bacterium Mycobacterium smegmatis as well as from E. coli following heterologous expression. Mycobacterial inverted membrane vesicles (IMVs) will be prepared from M. smegmatis. EtfD activity assays will make use of Mtb EtfD and will be performed in 384 well plate format. A proprietary library of compounds that kills Mtb in fatty acid medium will be made available by collaborators at Calibr-Skaggs. Cryo-EM will be used to determine the atomic structures of EtfD bound to ETF and to novel inhibitors, guiding downstream medicinal chemistry optimization of the compounds.

Results. We have shown that butyryl-CoA prepared enzymatically in the laboratory can be used as a substrate in the place of commercially available butyryl-CoA in EtfD activity assays. This modification decreases the cost of experiments from ~$30/well to ~$1,50/well in 96-well plate assays. Initial attempts to overexpress recombinant mycobacterial ETF in E. coli were unsuccessful.

Discussion. Further optimization of the EtfD activity assay will focus on purifying over-expressed recombinant FadE5 and ETF proteins to use in assays. Solubility tags will be tested to improve the yield of ETF and decrease the cost of assay, enabling its use in high-throughput screens. Compounds identified by collaborators with phenotypic screens will be tested in this target-based assay. Structures of EtfD bound to ETF will enable rationale design of inhibitors that block their interaction

Poster #10

Post-Transcriptional Reprogramming by RNA-Binding Proteins in Pediatric AML Relapse

Shreya Kanade (Supervisor: Kristin Hope)

Introduction. Therapy advances have significantly improved the survival of childhood cancer patients. However, in the case of pediatric acute myeloid leukemia (pAML), remission remains a major challenge. The commonly used chemotherapy regimen of cytarabine, daunorubicin, and etoposide (ADE) is initially effective, but 30-40% of patients relapse with therapy-resistant disease and poor prognosis. This highlights the urgent need to identify molecular drivers of relapse and develop effective therapies. pAML is primarily driven by chromosomal rearrangements, most commonly KMT2A gene rearrangements (KMT2Ar), which generate oncogenic fusion proteins. Owing to its early onset, pAML has a relatively lower mutational burden than adult AML. This highlights the potential for a strong contribution of non-genetic mechanisms to disease progression. Post-transcriptional regulation, facilitated by the coordinated activity of RNA binding proteins (RBPs), can rewire gene expression in a stress-adaptive manner. This has been demonstrated across many cancer types, including by our own group in

adult AML. However, it is underexplored in pAML persistence. Our lab has compelling preliminary data that supports RBP involvement in pAML relapse.

Hypothesis. We hypothesize that chemotherapy-induced stress selects for RBPs that enable pAML progression and relapse. Our goal is to map key RBP-mediated post-transcriptional networks that sustain relapse and uncover targetable dependencies.

Methods. We will utilize our lab's expertise in CRISPR-screening and dissecting RBP-controlled networks via integrative multi-omics to 1) identify RBPs that are novel regulators of chemoresistance, and 2) define how they post-transcriptionally reprogram and sustain pAML. We have identified RBPs highly upregulated at relapse, and associated with poor patient outcomes from the TARGET AML pediatric RNA-sequencing dataset. These candidates will be evaluated as potential pAML dependencies under steady-state conditions and under ADE chemotherapy using pooled CRISPR-Cas9 sgRNA library screening in cord blood-derived KMT2Ar pAML transplanted into a murine model. Then, we will collect murine bone marrow and spleen at different time points from leukemia induction, throughout treatment, and until remission or throughout relapse. This will allow us to assess the importance of candidate RBPs in chemotherapy response. We will measure the level of engraftment and leukemic blast generation by flow cytometry, and perform histological analysis on collected tissues. After treatment, significantly depleted sgRNAs will indicate RBPs that are likely key regulators of chemotherapy resistance. Finally, mechanistic studies will focus on the top candidate, selected based on level of depletion, and known involvement in pAML-relevant pathways. We will combine unbiased global approaches such as eCLIP to identify which RNAs are bound by the RBP, and proteomic analyses to identify whether those RNA interactions impact protein levels. Thus, we will define novel therapeutic targets and map relapse-supportive post-transcriptional regulatory networks.

Conclusion. The increasingly druggable network of RBPs controlling adaptive gene expression changes is untapped as an anti-leukemic therapeutic option. This project will provide critical insights into non-genetic drivers of pAML relapse and therapy resistance. Our data will identify biomarkers of relapse risk and novel avenues for precision therapies aimed at overcoming pAML relapse

Poster #11

Investigating VSIG10L as a biomarker for IAP antagonists in squamous cell carcinomas of the upper aerodigestive tract

Danae Rin Chen (Supervisor: Scott Bratman)

Introduction. Radiotherapy serves as a cornerstone of definitive treatment of squamous cell carcinoma of the upper aerodigestive tract (SCC-UADT), but radioresistance is a prevalent concern. Inhibitor of Apoptosis Proteins (IAPs) block cell death pathways and are often overexpressed in SCC-UADT, positioning IAP antagonists as a promising class of radiosensitizers. Currently, four IAP antagonists, including Xevinapant, Birinapant, Tolinapant, and LCL-161, are in clinical development as radiosensitizers for SCC-UADT. Given the molecular heterogeneity of SCC-UADT, it is likely that only specific tumor subsets are susceptible to IAP antagonist-mediated radiosensitization. Without predictive biomarkers to guide patient selection for IAP antagonists, treatment of patients must be empiric. This approach may limit overall therapeutic efficacy and hinder the clinical translation of IAP antagonists. We earlier identified VSIG10L as a promising predictive biomarker candidate through an integrative analysis of tumor cell line pharmacogenomic screens and clinical cancer transcriptomics data. Here, we will elucidate the molecular underpinnings of VSIG10L to address a critical knowledge gap essential for its clinical translation as a biomarker.

Methods. We selected two SCC-UADT cell lines based on high VSIG10L expression in transcriptomic screens, GDSC and CCLE. The radiosensitization efficacy of four IAP antagonists, as mentioned above, was compared using multiplexed phosphatidylserine exposure and membrane integrity assays, followed by CellTiter-Glo assay after 9 days. We calculated the area under the curve (AUC) to quantify cellular response to multiple doses of IAP antagonist and ionizing radiation. VSIG10L was silenced using RNA interference in cells. Sensitization to IAP antagonists was quantified using CellTiter-Glo. We curated a panel of candidate interaction partners of VSIG family members. The VSIG10L interactome was characterized using RT-qPCR screens of this curated panel after VSIG10Lknockdown and validated by targeted Western Blot in subcellular fractions. In situ endogenous VSIG10L-protein interaction was evaluated by Duolink Proximity Ligation Assay and visualized by immunofluorescence.

Results. Of the four IAP antagonists tested, Birinapant and Xevinapant both induced more programmed cell death after low-dose radiation. Birinapant induced the greatest enhancement in radiosensitivity. VSIG10L knockdown sensitized SCC-UADT cells to cell death induced by all IAP antagonists. VSIG10L knockdown also resulted in significant upregulation of AXLtranscript and protein expression. We observed that VSIG10L and AXL proteins were co-localized in the nuclear fraction of cells, consistent with a potential for physical proximity and binding in situ. VSIG10L stable knockdown cell lines were generated for ongoing functional characterization.

Conclusion. Our results suggest that VSIG10L expression is a determinant of resistance to IAP antagonists, possibly through a VSIG10L-AXL axis that functions as a molecular rheostat of IAP antagonist-mediated programmed cell death. AXL is a receptor tyrosine kinase that regulates cell survival and proliferation. AXL can negatively regulate necroptosis, a programmed cell death mode that may promote tumor repopulation after radiotherapy by enhancing IL-8 secretion. Deciphering the functional mechanisms of VSIG10L-mediated therapeutic resistance may reveal novel strategies to sensitize tumor cells to IAP antagonists and ultimately, radiotherapy.

Poster #12

An IRE powered in situ vaccination strategy against locally aggressive prostate cancer

Evgenija Serafimova (Supervisors: Keith Lawson & Hansen He)

Prostate cancer remains the most common malignancy among men, with high-risk cases frequently progressing to metastatic disease and exhibiting resistance to conventional therapies, including surgery, radiation, and androgen deprivation. A major clinical challenge in these patients is the presence of micrometastatic disease at the time of primary tumor treatment, stressing the need for therapeutic strategies that not only achieve local tumor control but also elicit systemic anti-tumor immunity.

Irreversible electroporation (IRE) has emerged as a promising nonthermal ablative modality that induces immunogenic cell death through mechanisms such as necroptosis and pyroptosis while preserving surrounding tissue architecture. Preclinical studies demonstrate that IRE promotes a pro-inflammatory tumor microenvironment (TME), characterized by tumor antigen release and dendritic cell activation, thereby facilitating the priming of adaptive immune responses. IRE's immune-enhancing properties and favourable safety profile position it as an ideal partner for combination immunotherapy, with the potential to overcome key barriers in limiting treatment success including low and heterogeneous neoantigen burden, poor immune infiltration, and an immunosuppressive TME.

First, to elucidate the molecular mechanisms underlying IRE-induced immune activation and identify determinants of tumor response, genome-wide CRISPR knockout and interference (CRISPRi) screens will be performed in immunocompetent prostate cancer models. Mouse prostate cancer cell lines engineered to express Cas9 or dCas9 will be transduced with lentiviral sgRNA libraries targeting the mouse genome and subjected to IRE at defined cytotoxic thresholds. Changes in sgRNA representation will be quantified by next-generation sequencing (NGS) to identify genes regulating immunogenic cell death and tumor survival. In vivo CRISPR screens will be conducted in syngeneic C57BL/6 mouse models of prostate cancer to validate that our results generalize to the context of an intact tumor microenvironment. Computational analyses will be used to identify genes enriched or depleted after treatment, providing insights into the genes pathways governing IRE-driven immunogenic cell death.

Second, we propose a novel focal immunotherapy strategy for aggressive localized prostate cancer that integrates IRE with a lipid nanoparticle-encapsulated mRNA-based neoantigen vaccine (LNP-mRNA vaccine). Mechanistically, this combination is designed to enhance anti-tumor immunity by: (i) delivering selected immunogenic neoantigens that may be insufficiently expressed or released following IRE alone, (ii) enabling efficient cytosolic expression of neoantigens in dendritic cells to promote antigen presentation, and (iii) providing intrinsic adjuvant effects through ionizable lipids within the LNP formulation. Together, this approach aims to synergistically amplify local and systemic immune responses, offering a promising strategy to improve outcomes in patients with high-risk prostate cancer.

Poster #13

Characterizing the role of the miR-181/135 families in neuroendocrine tumor phenotypic plasticity

Sylvia Cheng (Supervisors: Iacovos Michael & Hansen He)

Background. Neuroendocrine tumors (NETs) are a heterogeneous group of malignancies originating from neuroendocrine cells of various tissues or through the trans-differentiation of adenocarcinomas after chemotherapy. Around one-fifth of all NET patients are diagnosed with metastasis and ultimately have a 5-year survival of only ~20-30%; despite therapeutic advancements, metastatic NETs are invariably lethal. Therefore, there is an urgent need to understand the mechanisms behind NET progression and metastasis.

Cancer phenotypic plasticity is the de-differentiation and/or trans-differentiation of transformed cells, and is a mechanism of acquired therapy resistance, invasiveness, and metastatic potential in NETs. Literature suggests the transition of pancreatic NETs (PanNETs), small-cell lung cancer (SCLC), and neuroendocrine prostate cancer (NEPC) into aggressive subtypes involves taking on a neuron-like phenotype.

Micro-RNAs (miRNAs) are a class of small, non-coding RNAs that are critical regulators of cellular identity in cancer. The miRNA-181 and -135 families are known regulators of neuronal identity. Our results showed upregulated expression of miR-181/-135 in high-grade PanNET mouse tumors and metastatic lesions, and overexpression (OE) of miR-181 induced expression of neuronal gene sets and axonal protrusions in PanNET cells in vitro, which are important for invasion. Currently, the regulatory networks governing neuronal mimicry and its role in NET progression are largely unknown. To identify the role of the miR-181/-135 families in NET phenotypic plasticity and regulating neuronal identity, we hypothesize that miR-181/-135 regulates neuronal gene circuits during phenotypic plasticity to give rise to therapy-resistant, aggressive NET subtypes.

Objectives. 1) Characterize the effects of miR-181/-135 OE and knockout (KO) on NET cell phenotype. OE and KO will be performed in PanNET, prostate cancer, lung cancer cell lines. In vitro cell proliferation, invasion, and metastasis assays will assess functional consequences of miRNA expression and loss. In vivo tumor formation, and brain and liver metastasis will be quantified as functional readouts of miRNA activity. 2) Identify the miR-181/-135 target genes and characterize their role in NET plasticity. Bulk total-RNA-seq will be performed on OE and KO cells and, with mouse and human NET transcriptomic data, candidate miR-181/-135 gene targets will be identified using our Bio-miRTa algorithm10. These gene targets will be validated using in vitro and in vivo functional and reporter assays for their role in NET plasticity and neuronal cell phenotype.

Significance. Delineating the mechanisms that govern NET phenotypic plasticity, and metastasis is critical for identifying new, promising therapeutic targets for NET patients with metastatic disease.

Poster #14

X2CT-CLIP: Early molecular patterns of TP53 loss of heterozygosity in Li-Fraumeni Syndrome

Hailey Stack (Supervisor: David Malkin)

Li-Fraumeni syndrome (LFS) is a hereditary cancer-predisposition disorder caused by germline TP53 mutations. Mutant p53 disrupts DNA-damage repair and cell-cycle control, leading to an elevated cancer risk of ~40% by adolescence and nearly 100% over a lifetime. Recent work showed that 86% of LFS tumors exhibit loss of the wild-type (WT) TP53 allele (loss of heterozygosity (LOH)), an alteration not observed in healthy tissues. Importantly, LOH appears to arise years before tumor diagnosis, likely during prenatal or early postnatal development, implicating it may be an early driver of clonal evolution in LFS. While TP53 LOH is well characterized in sporadic cancers with somatic TP53 mutations, its role in LFS malignant progression remains poorly understood. To address this, we leverage LFS patient-derived dermal fibroblasts collected either years before or after cancer diagnosis. Using droplet digital PCR, we quantify WT and mutant TP53 allelic ratios over time in culture. Fibroblasts collected after a patient's cancer diagnosis show a significant enrichment of the mutant allele, suggesting possible WT TP53 loss, compared fibroblasts obtained before diagnosis maintained stable allelic balance. Single-cell RNA sequencing (scRNA-seq) will be applied to uncover transcriptional changes across cells with or without allelic imbalance. This will enable identification of changes in gene-expression and biological pathways altered throughout clonal evolution. These LOH-associated signatures will then be mapped to scRNA-seq data of tumors and matched muscle in a Trp53R172H/+ LFS mouse model, determining whether any of these signatures occur throughout tumor evolution in vivo. Collectively, this project will generate the first allelic-transcriptomic map of clonal evolution in LFS fibroblasts, providing insight into the earliest steps of tumor evolution. By uncovering pathways uniquely disrupted across cell states, we aim to identify mechanistic drivers of early malignant susceptibility and highlight potential windows for cancer prevention or interception in LFS.

Poster #15

Identifying essential factors for SRSF2^{P95H} CHIP mutation expansion

Keheng (Tina) Wang (Supervisor: Kristin Hope)

Clonal hematopoiesis (CH) is a pre-malignant state initiated when a hematopoietic stem cell (HSC) acquires a mutation that confers the cell a competitive advantage. This process leads to an abnormal clonal expansion of the mutant HSC, resulting in a 10-fold increased risk of hematologic malignancies, including acute myeloid leukemia. Understanding CH is essential to the development of early interception strategies to prevent malignant transformation in these CH-associated high-risk patients.

Serine and Arginine-rich Splicing Factor 2 (SRSF2) is an RNA-binding protein that regulates pre-mRNA splicing, playing an important role in protein isoform expression. A proline-to-histidine mutation (P95H) that alters the splicing activity of SRSF2 is one of the most common CH driver mutations. SRSF2^{P95H} cells expand at a later age, but induce the most rapidly expanding clone among all CH-associated mutations, with a particularly high risk of leukemogenesis and malignant progression. However, previous research has shown that HSCs with the SRSF2^{P95H} mutation alone have a reduced competitive advantage, suggesting additional extrinsic factors contributing to SRSF2^{P95H} mutant expansion. Mesenchymal stromal cells (MSCs) in the bone marrow (BM) provide a supportive niche for HSCs. In a perturbed state such as aging and leukemia, MSCs can undergo reprogramming that leads to functional and phenotypic changes. For instance, MSCs lose osteogenic differentiation capabilities and facilitate an inflammatory microenvironment during aging. Despite these observations, it is not known whether and how BM MSCs can support the clonal expansion of SRSF2^{P95H} mutants. I therefore hypothesize that the altered MSCs act as a supportive extrinsic factor that selects for SRSF2^{P95H} HSCs and induces their clonal expansion, and that this is a contributing mechanism of SRSF2^{P95H} CH establishment and a potential axis for leukemia interception.

Firstly, we will use CRISPR-Cas9 technology to generate the heterozygous SRSF2^{P95H} mutation in BM-derived CD34+ HSCs through homology-directed repair (HDR). Cell viability and HDR efficiency of edited cells will be measured. To assess the effects of BM MSCs on expanding SRSF2^{P95H} HSCs, an in vitro 3D biomimetic scaffold-based culture system will be used to co-culture MSCs and edited HSCs. The proportion of SRSF2-edited cells from the input and output populations will be analyzed by Sanger sequencing and Synthego ICE analysis, then compared between different conditions to identify factors that induce a more exaggerated expansion of mutant cells. Additionally, I will perform immunophenotypic analysis of these co-cultures by flow cytometry to determine which conditions promote a signature of increased stem and progenitor output and reduced lineage differentiation, both of which are common features of CH-associated hematologic malignancies.

This project aims to identify extrinsic factors from the BM MSC niche supportive of SRSF2^{P95H} CH. This finding will deepen our understanding of CH and potentially provide an avenue for preventing CH-associated malignancies during aging.

Poster #16

Multi-Agent System for Circular RNA Biomarker Research, Discovery and Prioritization

Jiaru (Caroline) Ni (Supervisors: Hansen He & Benjamin Haibe-Kains)

Circular RNAs (circRNAs) are an emerging class of regulatory non-coding RNAs increasingly implicated in cancer through mechanisms including microRNA sponging, protein scaffolding, and modulation of parental gene expression. Despite their growing biological relevance, existing computational pipelines remain fragmented, largely adapted from linear RNA workflows, and poorly suited to circRNA-specific challenges such as high sequence similarity with linear counterparts, low expression abundance, and off-target susceptibility. Critically, current biomarker prioritization strategies rely almost exclusively on static differential expression signals, with minimal integration of functional perturbation evidence or clinical annotation — creating a significant gap between circRNA discovery and clinical translation. To address these limitations, we propose a large-language model (LLM) based multi-agent system (MAS) for accelerating circRNA biomarker discovery and clinical translation in precision oncology, organized across two functional layers. The first layer supports circRNA research and knowledge integration by unifying perturbation-derived experimental evidence, clinical sample annotations, and agent-executed analytical results with mechanism-grounded interpretations drawn from curated biomedical literature. The second layer leverages this integrated, multi-evidence representation to drive hypothesis generation and ranking for principled biomarker prioritization. Systematic benchmarking against single-agent baselines and ablation studies will be conducted to quantify the contribution of each evidence source and evaluate overall framework robustness. Collectively, this work establishes the first agentic framework specifically designed for mechanistically informed circRNA biomarker prioritization, offering improvements in reliability, interpretability, and clinical grounding of candidate rankings. The resulting system is expected to accelerate the identification of circRNAs with genuine regulatory and clinical significance, supporting their translation into robust and actionable cancer biomarkers. Our MAS follows a hieratical structure, consists of a supervisor agent with five subagents with specialized tools and tasks. Preliminary implementation demonstrates successful automation of end-to-end junction targeting circRNA knockdown design workflows for siRNA, shRNA and Cas13d approaches; integrated viennaRNA package (cite)for RNA structure prediction, comparison and design; significantly accelerating circRNA researcher workflows. Private and public circRNA databases, screening studies, and clinical samples have been integrated into the MAS as a unified knowledge base, supporting downstream biomarker discovery, functional prioritization, and serving as an interactive resource for researchers. The framework will be systematically benchmarked against single-agent baselines, with ablation studies to quantify each evidence source's contribution and assess overall robustness. Future development will focus on grounding candidate rankings in functional and clinical context, enabling the system to surface circRNAs of genuine biological relevance rather than expression-driven artifacts. This work establishes the foundation for the first agentic framework specifically designed for mechanistically informed circRNA biomarker prioritization. By unifying knockdown design, mechanistic interpretation, and multi-evidence ranking into a coherent autonomous system, this framework is expected to improve the reliability and interpretability of circRNA candidate selection, ultimately accelerating the translation of circRNA research into robust and clinically actionable cancer biomarkers.

Poster #17

Biophysical Enhancement of Radiation-Activated Photodynamic Therapy (radioPDT) forBrain Tumor Models

Manjusha Muralidharan (Supervisor: Deepak Dinakaran)

Background. Radiation-activated photodynamic therapy (radioPDT) uses X-ray-excited nano-scintillators to activate photosensitizers deep within tissue, generating cytotoxic reactive oxygen species independent of receptor expression. Unlike ligand-targeted nanoparticles, radioPDT represents a biophysical therapeutic strategy particularly suited for heterogeneous and treatment-resistant tumors such as glioblastoma (GBM). However, translation of nanoparticle-based therapies to the brain is limited by the blood-brain barrier (BBB), which restricts particle penetration. Physical modulation of the tumor microenvironment using focused ultrasound (FUS) and microbubble cavitation can transiently alter vascular permeability and enhance nanoparticle delivery without relying on biochemical targeting. To bridge mechanistic validation and translational relevance, we designed an integrated pipeline combining peripheral tumor studies with planned orthotopicGBM to evaluate how physical forces influence radioPDT efficacy.

Methods. In Phase I, mechanistic proof-of-concept studies were performed in immunodeficient SCID mice bearing PC3 prostate cancers in flank xenografts. Animals were assigned to control, radiation alone (RT), nanoparticle plus radiation (radioPDT), or radioPDTand ultrasound-stimulated microbubbles (radioPDT+USMB). Tumors were analyzed using multiplex immunofluorescence to assess proliferation and apoptosis (Ki67, cleaved caspase-3), oxidative stress and PDT injury (4-HNE, TUNEL), vascular architecture (CD31, NG2), hypoxia (CA9, HIF-1α), and inflammatory infiltration (CD45, Iba1). These studies were designed to define how biophysical approaches—rather than receptor-mediated uptake—shape nanoparticle distribution, vascular effects, oxidative injury, and overall radioPDT potency.
In Phase II, translational GBM in-vivo models using luciferase-transfectedU87 and U251 cell lines in SCID mice will enable longitudinal tumor monitoring via bioluminescence imaging, with planned integration of FUS-mediated BBB modulation. This will be replicated using patient-derived GBM cell lines to create a PDX model.

Results. PC3 xenograft studies demonstrates that combination radioPDT+USMB significantly remodeled tumor vascular architecture. CD31 staining demonstrated marked endothelial disruption and reduced micro vesseldensity, while NG2 expression revealed pronounced pericyte detachment, indicating loss of vessel stabilization and vascular integrity,suggesting synergistic vascular destabilization. This vascular collapse was accompanied by increased apoptosis (TUNEL). Hypoxia markers (HIF-1α, CA9) indicated dynamic oxygen modulation, supporting radiation sensitization and reduced tumor adaptability.

Conclusions. Our findings supportradioPDT+USMBinduces coordinated vascular disruption, oxidative injury, and DNA damage, leading to enhanced tumor cell death. This is a biophysical therapeutic paradigm in which mechanical modulation of tumor vasculature enhances radiation-activated photodynamic therapy (radioPDT) independent of tumor-specific receptor targeting. The observedvascular destabilization and impaired tumor perfusionis expected to improve BBB penetrance in orthotopic GBM models. This vascular remodeling amplifies oxidative stress, and enhances apoptotic cell death while limiting hypoxia-mediated adaptive responses.

Poster #19

Characterizing the role of HMGB3 in modulating tumour-immune interaction in brain metastasis.

Areeba Qureshi (Supervisor: Iacovos Michael)

Introduction. Brain metastases, most commonly arising from lung, breast, and melanoma cancers, are associated with poor prognosis and have limited therapeutic options. A major challenge in treating these tumours is understanding how disseminated cancer cells adapt to the unique brain microenvironment. High Mobility Group Box 3 (HMGB3), a non-histone chromatin-binding protein, has been implicated in tumour progression and immune modulation across multiple cancer types. Analysis of RNA-sequencing data demonstrates that HMGB3 is significantly upregulated in brain metastasis compared to matched primary breast tumours, and its expression correlates with poor patient survival. Notably, recurrent tumours emerging from dormancy in immunocompetent Tol mice exhibited elevated HMGB3 expression, supporting its role in tumour adaptation under immune-selective pressure. Based on these findings, I hypothesized that HMGB3 promotes brain metastasis by modulating tumour-immune interactions, enabling cancer cells to adapt to immune-selective pressures within the brain.

Methods. To investigate the role of HMGB3 in tumour progression and immune modulation, a constitutive HMGB3-overexpressing lentiviral construct was generated and transduced into E0771 murine breast cancer cells, which express low endogenous HMGB3. Intracranial injections were performed in both immunocompetent Tol mice and immunocompromised SCID mice. Tumour growth was monitored over time using bioluminescence imaging. At the endpoint, survival analysis and histological characterization were conducted.

Results. HMGB3 overexpression enhanced tumour growth in immunocompetent Tol mice, demonstrated by a robust increase in bioluminescence signal relative to control mice. This was accompanied by a marked reduction in survival, with the HMGB3-overexpressing cohort reaching endpoint significantly earlier than controls. In contrast, this phenotype was completely abolished in immunocompromised SCID mice, where no significant differences in tumour growth or survival were observed between HMGB3-overexpressing and control groups. These findings indicate that HMGB3-driven tumour progression is dependent on an intact adaptive immune system.

Discussion. Together, these results support a model in which HMGB3 promotes brain metastasis through modulation of thetumour-immune microenvironment. The loss of its tumour-promoting effects in immunocompromised settings highlights a critical dependence on adaptive immunity, suggesting that HMGB3 may facilitate immune evasion. Elevated HMGB3 expression in recurrent tumours further indicates a role in enabling tumour persistence and outgrowth following immune-mediated constraint. Ongoing studies will define how HMGB3 shapes immune cell composition and function within the brain tumourmicroenvironment.

Conclusion. This work provides important insight into the interaction between epigenetic regulation of cancer cells and the tumour-immune microenvironment, and may inform the development of combinatorial therapies that simultaneously target immune evasion and metastaticprogression.

Poster #20

Integrating genetic mutations and DNA methylation in cell-free DNA to identify novel biomarkers and detect minimal residual disease in lymphoma

Uditha Maduranga Heeralu Pathirannahalage (Supervisor: Robert Kridel)

Introduction. Relapse occurs in 30–40% of diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (FL) patients despite treatment advances, with minimal residual disease (MRD) detection emerging as a critical prognostic indicator. Current circulating tumor DNA (ctDNA)-based MRD detection approaches rely on single modalities, such as somatic mutation profiling or DNA methylation analysis, each with limitations in sensitivity and specificity. We hypothesized that integrating somatic variants with lymphoma-specific methylation markers would improve MRD detection compared to single-modality approaches.

Methods. The overarching objective of this study was to enhance the evaluation of treatment response in lymphoma by developing and validating a standardized, highly sensitive, dual-omic ctDNA assay integrating genetic variants with lymphoma-specific methylation markers. A three-phase translational approach will be employed. First, a validated panel of lymphoma-specific methylation markers present in both tumor tissue and plasma will be established. Next, a standardized dual-omic panel integrating these methylation markers with published recurrent somatic variants will be constructed, and per-patient detection profiles will be characterized using targeted Illumina 5-base sequencing of baseline plasma samples. Finally, applying the dual-omic panel to end-of-treatment and surveillance plasma samples will enable correlation of MRD status with PET/CT response and survival outcomes.

Discussion & Conclusion. This novel liquid biopsy assay enables earlier and more accurate detection of minimal residual disease while reducing the false positives and negatives associated with PET imaging. Beyond clinical translation for improved lymphoma management, this work provides a generalizable framework for dual-omic ctDNA detection applicable to other hematologic malignancies and solid tumors.

Poster #21

Evaluation of the 2009 Canadian Retinoblastoma Strategy and Its Translationto a Living Guideline Framework

Brandon Hoang Tat (Supervisor: Brenda Gallie)

In high-income countries, retinoblastoma (Rb) is a highly curable intraocular cancer; however, early screening, diagnosis, and treatment are critical for achieving successful outcomes. As a rare disease, many primary care settings lack the knowledge and resources required for timely recognition and management, and access to specialized Rb care is often limited, resulting in varying quality of care. To address the challenges of Rb care, the Canadian National Retinoblastoma Strategy (CNRbS) was published in 2009 to standardize care, improve early detection and referral, and enable consistent clinical reporting. However, a comprehensive systematic review of its long-term clinical and system-level impact is lacking. Without evaluation, it is unclear which elements of the CNRbS were most effective and whether observed improvements in outcomes can be directly attributed to the strategy or to advancements in therapies. Given these gaps, developing a framework to evolve the CNRbS into a living guideline (LG) model offers a strategic approach to address guideline obsolescence. LGs enable continuous updating of evidence to accelerate adoption of best practices and integration of new knowledge, improving Rb care. The objective of this research is to assess the clinical and system-level outcomes following the 2009 CNRbS and devise an empirically informed model for its transformation into an LG. This project will use a mixed-methods approach, combining quantitative evaluation of changes in clinical presentation, management, and outcomes following implementation of the CNRbS with qualitative assessment of current standards of care and implementation processes. Quantitative analyses will draw on clinical registry and hospital record data to compare patterns of care before and after CNRbS implementation, while qualitative analyses will incorporate perspectives from key stakeholders, including clinicians, patients, and policymakers, to identify barriers and facilitators to effective implementation. Findings from these analyseswill inform an LG model integrating current evidence with real-world outcome data and stakeholder input. The LG framework will be designed to support continuous guideline updating and sustained implementation of best practices in Rb care.This research will provide the first comprehensive evaluation of the CNRbS andidentify structural and system-level factors influencing long-term implementationand effectiveness of guidelines. These contributions will strengthen pediatric oncology policy, improve patient outcomes, and support the maintenance of an evidence-based healthcare system.

Poster #22

Neuroimaging to uncover genetic determinants of chemotherapy-induced neurotoxicity

Kingsley Yong (Supervisor: Brian Nieman)

Introduction. Acute lymphoblastic leukemia (ALL), the most commonly diagnosed childhood cancer in Canada, has a >90% survival rate largely due to intensive chemotherapy regimens. However, 40-60% of cancer survivors treated with chemotherapy experience lifelong cognitive impairments affecting memory, attention, and social behaviour. Survivors of ALL perform worse than healthy peers on measures of processing speed and working memory, and magnetic resonance imaging (MRI) reveals widespread brain volume reductions of up to 6% in some regions. These neurocognitive late effects substantially impair long-term quality of life. Importantly, there is marked inter-individual variability in the severity of these outcomes, with some survivors far more affected than others. Identifying individuals at greatest risk would enable early, targeted interventions to mitigate these effects.

At present, there is no reliable way to predict susceptibility to chemotherapy-induced neurotoxicity. Evidence suggests that genetic differences are a major contributor to the observed variability in outcomes. Ideally, a genome-wide association study (GWAS) in a large survivor cohort would be used to identify relevant genetic variants. However, the relatively low incidence of ALL makes it impractical to recruit enough participants for a sufficiently powered human study. As an alternative, I propose a genome-wide analysis using a mouse model. We have previously shown that mice treated with the ALL chemotherapeutic agents methotrexate (MTX) and vincristine (VCR) exhibit widespread brain volume changes measured by MRI, mirroring findings in humans.

To investigate genetic factors that mediate susceptibility or resilience to MTX- and VCR-induced neurotoxicity, I will use a panel of recombinant inbred mouse lines known as the BXD lines. These lines introduce controlled genetic diversity, and their fully characterized genomes enable high-resolution genetic mapping. Variation in brain structure across lines following chemotherapy will allow identification of quantitative trait loci (QTLs) associated with sensitivity or resilience to treatment-induced neurotoxicity.

Aim. Identify QTLs associated with chemotherapy-induced neurotoxicity using MRI-based phenotyping in BXD mouse lines.

Hypothesis. MTX- and VCR-treated mice will exhibit brain volumetric changes relative to controls, with variability across BXD lines. QTL analysis will identify genetic loci associated with these changes.

Methods. Mice will be assigned to MTX (10 mg/kg), VCR (1 mg/kg), or control (saline) groups. Treatments will be administered intravenously at postnatal days (P) 17 and 19, corresponding to childhood development. Mice will be monitored and weighed daily. At P63 (early adulthood), mice will be perfusion-fixed and prepared for ex vivo MRI. Power analyses indicate that six mice per sex per line per treatment group across approximately 60 lines will provide 80% power, yielding a minimum sample size of 2160 mice. Imaging will be conducted using a custom 24-coil array on an 11.7-T MRI scanner, allowing simultaneous scanning of 24 brains. Images will be processed using an automated pipeline that segments the brain into 183 structures. Structural phenotypes will be linked to known genomic markers using QTL analysis with linear mixed modelling.

Poster #23

Identifying Tumour Antigens using Patient-Derived Models to Develop Personalized Cancer Vaccines for Small Cell Lung Cancer Patients

Olivia Huang (Supervisor: Hansen He & Benjamin Lok)

Introduction. Small cell lung cancer (SCLC) is a highly aggressive neuroendocrine carcinoma characterized by rapid proliferation and early metastasis. Approximately two-thirds of patients present with metastatic disease at the time of diagnosis, with a five-year survival rate of less than 10%. Despite initial response to first-line therapy, nearly all SCLC patients relapse within 6 to 12 months, underscoring the need for novel therapies that induce durable anti-tumour responses.

Personalized cancer vaccines have emerged as a promising immunotherapeutic modality due to their ability to simultaneously target multiple tumour antigens and generate long-lasting immunological memory. SCLC exhibits one of the highest tumour mutational burdens among human cancers, providing a large pool of tumour antigens for designing cancer vaccines. However, the identification of these antigens is challenging in SCLC due to downregulation of major histocompatibility complex class I (MHC-I) molecules. Recent studies have demonstrated that MHC-I expression can be restored by targeting epigenetic regulators such as EZH2 and LSD1, but their influence on antigen diversity remains unclear. I hypothesize that inhibiting EZH2 and LSD1 will increase both the abundance and diversity of peptides presented on MHC-I molecules in SCLC, thereby enabling more effective identification of targetable tumour antigens for cancer vaccine development.

Methods. Immunopeptidome and comprehensive genome profiling will be performed on SCLC patient-derived organoids (PDOs) and patient-derived xenografts (PDXs) following MHC upregulation, integrating mass spectrometry (MS), whole genome sequencing (WGS), and RNA sequencing (RNA-seq). WGS will also be conducted on patient-matched peripheral blood leukocytes to filter out germline variants. Tumour antigen candidates will then be identified using computational pipelines and stratified into one of three tiers: 1) detected by both MS and RNA-seq; 2) detected by MS only; 3) detected by RNA-seq only. In silico MHC-I binding prediction will be performed to prioritize high-affinity peptides for experimental validation. The immunogenicity of top-ranked tumour antigens will be assessed in vitro using the IFN-γ ELISpot assay and PDO-T cell co-culture systems. Humanized mouse models will also be used to validate the immunogenicity of tumour antigens by assessing tumour shrinkage, T cell infiltration, and the generation of memory T cells.

Results. RNA-seq analysis of three SCLC cell lines (SBC5, H1048, H82) identified over 14,000 non-canonical transcripts, the majority of which were generated from alternative splicing at known gene loci. However, only a small subset of transcripts was expressed at levels sufficient for antigen presentation. Among these transcripts, only a small proportion of peptides, primarily 8-12 amino acids in length, were detected by MS.

Conclusion. Despite high TMB, the identification of tumour antigens for vaccine development is limited by low MHC-I expression in SCLC. This study investigates strategies to expand the repertoire of tumour antigens by targeting epigenetic regulators of MHC-I, providing insights into the possibility of combining epigenetic modulators with immunotherapies. Moreover, by leveraging patient-derived models, the tumour antigens identified from this study have the potential to accelerate the development of next-generation immunotherapies, including cancer vaccines.

Poster #24

Investigating Cellular Responses of Hematopoietic Stem and Progenitor Cells to GLP-1 Receptor Agonists in Pre-Cancerous Humanized Mouse Models

Isabella Di Biasio (Supervisor: Stephanie Xie)

Clonal hematopoiesis (CH) is an age-associated condition in which hematopoietic stem and progenitor cells (HSPCs) acquire somatic mutations, most commonly in DNMT3A and TET2 genes, leading to clonal expansion and a 10-fold increased risk of blood cancers, including acute myeloid leukemia (AML). Chronic inflammation and metabolic conditions, such as obesity, are thought to play a central role in the expansion of these mutant HSPCs. High fat diet (HFD)-induced inflammation represents a clinically relevant yet underexplored modifier of accelerated CH expansion HFD models in mice have been shown to enhance the fitness of DNMT3A mutant clones, and epidemiologic studies have linked metabolic health to CH prevalence and adverse outcomes. Our laboratory has shown mutant HSPCs are tolerant of an inflammatory milieu, and inflammatory cytokines such as TNFα promote the expansion of DNMT3A and TET2 mutant HSPCs. Disruption of this inflammatory feedback loop represents a promising therapeutic strategy. Glucagon-like peptide-1 receptor agonists (GLP-1RAs), such as semaglutide, exhibit anti-inflammatory effects and are linked to reduced incidence of hematologic cancers in patients with type 2 diabetes. However, whether GLP-1RAs can mitigate CH-driven expansion remains unknown.

Here, we use humanized mouse models of CH to investigate the impact of inflammation and GLP-1RA treatment on clonal expansion and inflammatory responses. We have established protocols to model TET2- and DNMT3A-CH in immunodeficient mice using CRISPR-edited human CD34+ HSPCs. To assess acute inflammatory responses, mice were pre-treated with semaglutide or vehicle control prior to administration of a septic dose of lipopolysaccharide (LPS). Peripheral blood was collected for plasma multiplex cytokine analysis to evaluate systemic inflammatory responses. Ongoing work extends this model to chronic metabolic inflammation, where mice are placed on either a high fat diet (HFD) or control diet (CD), followed by longitudinal assessment of clonal expansion and immune profiling. Initial results demonstrate that this model can be used to assess the effect of GLP-1RA treatment on inflammatory responses in vivo. In an in vivo xenograft model of wild-type NSG mice, semaglutide pre-treatment prior to LPS challenge reduced the inflammatory milieu compared to LPS alone, including lower levels of human TNFα as measured by plasma multiplex cytokine assay. These findings recapitulate observations in syngeneic mouse models and demonstrate that GLP-1RA treatment can attenuate acute inflammatory stress in vivo. These findings support a model in which GLP-1RA-mediated suppression of inflammatory signaling may alter the hematopoietic environment that supports mutant HSPC expansion. Given that mutant HSPCs are tolerant of inflammatory conditions, reducing inflammatory cues may diminish their competitive advantage. Ongoing studies are investigating whether chronic HFD-induced inflammation enhances DNMT3A and TET2 mutant clonal expansion, and whether GLP-1RA treatment can mitigate this effect. Together, this work demonstrates that GLP-1RA treatment attenuates acute inflammatory responses in vivo and establishes a foundation to test whether these effects translate to altered clonal dynamics in CH. Given their widespread clinical use, GLP-1RAs may represent a promising early intervention strategy for CH and hematologic malignancies.

Poster #27

Compact Representation of Pre-Calculated Monte Carlo for Efficient and Scalable Particle Transport Simulation

Iman Amini (Supervisor: Jan Seuntjens)

Introduction. Monte Carlo (MC) simulation is widely regarded as the most accurate method for modeling radiation transport in matter, but its high computational cost limits its use in time-sensitive clinical applications. Pre-calculated track Monte Carlo (PMC) methods address this limitation by reusing pre-generated particle tracks to accelerate dose calculations. However, PMC approaches require large track databases and may introduce uncertainties when stored tracks do not fully represent local physical conditions. Recent advances in artificial intelligence (AI) have shown promise in accelerating radiation therapy workflows, but many approaches replace physics-based models with purely data-driven predictions, potentially limiting interpretability and generalizability.

Methods. This work proposes an AI-enhanced PMC framework in which machine learning models are trained using high-fidelity Monte Carlo simulation data to learn the relationships governing particle transport. Specifically, models will be developed to capture dependencies between particle energy, direction, material properties, and energy deposition. These models will be integrated into the PMC framework to predict or interpolate particle track behavior, reducing reliance on large precomputed databases. The approach will first be developed for proton transport and subsequently extended to heavier ions such as carbon and helium. The framework will also be investigated for efficient estimation of Linear Energy Transfer (LET), an important quantity for assessing biological effectiveness in particle therapy.

Results. As this project is currently in the conceptual and preparatory stage, results are not yet available. Initial work focuses on dataset generation from MC simulations and the design of machine learning architectures for modeling particle transport behavior.

Discussion. By learning the underlying physics of particle transport rather than directly predicting dose distributions, this approach aims to preserve the accuracy and interpretability of MC methods while improving computational efficiency. The proposed framework may reduce dependence on large track databases and mitigate uncertainties associated with track reuse, addressing key limitations of existing PMC approaches.

Conclusion. This research aims to develop a hybrid physics-AI framework that combines the accuracy of Monte Carlo simulation with the efficiency of machine learning. If successful, it could enable faster and more scalable particle transport modeling and support advanced applications such as heavy-ion therapy and LET estimation.

Poster #29

Evaluating the Impact of Small Vessel Disease on Brain Health at Conventional (3T) and Low-Field (0.5T) MRI

Selena Gangaram (Supervisor: Bradley MacIntosh)

Background. Alzheimer's disease (AD) represents a major global health concern impacting nearly 40 million people around the world and remains the leading cause of dementia (Yiannopoulou & Papageorgiou, 2020). Recently, an anti-amyloid drug known as Lecanemab was approved in Canada as the first disease-modifying AD drug-based intervention (Alzheimer Society, 2026). Despite this advancement, individuals with significant underlying cerebrovascular pathology, particularly those with markers of cerebral small vessel disease (SVD) are more susceptible to adverse events compared to those without SVD. The presence of SVD can contribute to cognitive decline and can introduce treatment related complications that could hinder an individual from receiving anti-amyloid therapies (Zanon Zotin et al., 2021; Cummings et al., 2023). Moreover, white matter hyperintensities (WMH) are a key neuroimaging biomarker of SVD, which is a condition that contributes to cognitive decline, stroke, vascular dementia, and recognized as a co-driver of AD pathology (Duering et al., 2023; Zhuang et al., 2018). Currently, magnetic resonance imaging (MRI) is central to SVD detection and quantification, with WMH serving as a primary imaging marker (Zhuang et al., 2018). However, most scans are performed on conventional strength field scanners (i.e., 1.5T and 3T) which are costly and may limit access to care (Kravchenko et al., 2025; Zanon Zotin et al., 2021). As such, SVD's overlapping neurodegenerative and vascular pathology, emphasize the importance of improved vascular characterization to guide disease-modifying AD treatments.

Objectives/Methods. Aim 1 in this study seeks to evaluate the use of low-field 0.5T MRI to detect SVD as lower field strength scanners such as a 0.5T, provide sufficient gray matter and white matter contrast and offers less geometric distortion (Marques et al., 2019). Aim 2 will encompass the exploration of SVD's longitudinal impacts on cognition, leveraging the Alzheimer's Disease Neuroimaging Initiative (ADNI) dataset which will allow for the assessment of vascular contributions to neurodegeneration. Aim 1 will be tested by comparing structural images from individuals previously scanned on a 3T system, with newly acquired 0.5T scans from an EVRY MRI system. Both standardized visual rating scales (e.g. Fazekas rating scale) and automated image segmentation tools (e.g. FSL/Freesurfer) will be used to compare brain tissue volumes and other imaging-based markers. Scan-rescan reliability will be assessed using Interclass correlation tests where appropriate (volumetrics), Spearman rank tests for visual ratings, and DICE similarity index metrics when applicable to test for spatial congruency testing. Aim 2 will be tested using the Alzheimer's Disease Neuroimaging Initiative (ADNI) dataset. A Linear Mixed Effects model will be used to assess longitudinal WMH volumes over time and cerebral blood flow.

Significance: Through the comparison of low and conventional field strength MRI scanners, this study ultimately hopes to contribute to advances in brain health imaging. Demonstrating SVD detection on lower field strength scanners could elicit safer and equitable administration of disease-modifying AD therapies, while improving our understanding of vascular pathology in neurodegeneration. Through the analysis of longitudinal WMH data, SVD progression and how it relates to cognitive decline and overall AD pathology will be better understood.

Poster #30

Developing an AI Model to make Uncertainty-Quantified Predictions of Patient Specific Quality Assurance Scores for Radiotherapy

Rachel Cassidy (Supervisor: Thomas Purdie)

Introduction. Patient-Specific Quality Assurance (PSQA) is a necessary but resource-intensive step in the radiation therapy (RT) planning processthat quantifiesthe agreement between asimulated RT treatment plan and physicalradiation dosimetry measurements. Over the past 10 years, progress has been made in automating PSQA prediction using artificial intelligence (AI) models trained on RT plans (Ono et al., 2024), but clinical adoption has remained limited due in part to low verifiability of AI model output. Uncertainty quantification methods of AI have been demonstrated in RT planning tasks; however, the application of these methods to understand the confidence of automated PSQA prediction using AI remains limited (Hémon et al., 2025).

Methods. To determine the feasibility of enhancing automated PSQA verifiability, the deterministic uncertainty quantification approach ZigZag (Durasov et al., 2024) will be investigated. We will first train a baseline Gradient Boosting Decision Tree (uncertainty-unaware) AI model that predicts PSQA physical dosimetry measurements using previously developed beam delivery complexity metrics (McNiven et al., 2010) and radiomic features as input. A prototype model will be developed using approximately 2700 paired RT treatment plans and PSQA measurements acquired at our centre over a single year. After achieving satisfactory baseline performance evaluated using standard criteria (e.g. mean absolute error), we will apply the ZigZag approach to our model.

Conclusion. Our work aims to improve the verifiability of automated PSQA using AI by applying uncertainty quantification methods to a model trained on a large patient dataset. In addition to the direct clinical relevance of the translation of automated PSQA, this work also serves to investigate the transferability of uncertainty quantification methods to new tasks in RT. In this way, our work is a part of a broader effort to improve the reliability and transparency of AI in RT.

Poster #31

Experimental verification of waveguides for proton therapy

Carina Watson (Supervisor: Jan Seuntjens)

Introduction. One of the challenges with using radiotherapy for cancer treatment is the dose deposited to healthy tissue nearby the tumour. Proton therapy is an advanced form of radiotherapy that is able to reduce the radiation dose to tissue surrounding the tumour by 50-70%. However despite this advantage, proton accelerators required for proton therapy are large and expensive, limiting access. Canada currently has no proton therapy facilities.

Methods. Project IMPACT is designing a low-cost compact proton accelerator for proton therapy using a dielectric wall accelerator design. Circuit boards control the pulsing of voltage into waveguides that surround the beampipe, which create electric fields inside the beampipe to excite and accelerate the protons. This project involved two methods of verifying the functionality of these waveguides. Firstly, by measuring the waveguide's electric fields. Electrooptic sampling is used to experimentally test and measure the electric fields produced by the waveguide setup. This measurement method uses a sensitive electrooptic crystal that changes the polarization of a probe laser beam based on the electric field surrounding it. This eliminates issues with distorting currents produced in a probe cable when measuring electric fields with a basic probe. Additionally, electrooptic sampling will allow for the creation of a 3D map of the electric field during waveguide operation. Secondly, this project involves using beam physics simulation software to create a design for an electron proof-of-concept. Using a spare electron source, a basic electron accelerator using the waveguides will be made and tested. By using simulation tools, the design can be fine-tuned before being physically constructed. The electrons for the proof-of-concept will behave differently than the previously-simulated protons and need to be re-simulated. Since electrons are smaller particles than protons, electron drift away from the main beam axis, as well as drift due to external geomagnetic fields are a concern. Potential methods of containing the electrons include solenoids, magnets, or electrostatic plates.

Results and Discussion. There are no results yet of the electrooptic sampling to share. Initial results from the electron simulations show that the electrons will be able to be contained and directed before and after acceleration using electrostatic plates with kV level voltage, which is reasonable to build and operate.

Conclusion. Through verifying that the waveguides developed by the Seuntjens group function as expected, both in their produced distribution of electric field and in their ability to accelerate electrons, Project IMPACT can continue forward in designing a waveguide-based proton accelerator. This compact, low cost style of accelerator could allow for proton therapy to become more accessible in Canada and worldwide

Poster #32

Development of a TMS-Mounted Thin-Film Receive Coil for Concurrent TMS-FMRI

Julia Cosma (Supervisor: Fa-Hsuan Lin)

High-order cognitive functions, such as episodic memory, are supported by distributed neural networks rather than isolated brain regions. Non-invasive brain stimulation, specifically transcranial magnetic stimulation (TMS), holds significant potential for modulating these networks to mitigate memory decline in aging and neurodegenerative disease. However, the efficacy of TMS remains variable, as standard "open-loop" approaches lack physiological verification that pulses successfully engage deeper, functionally connected targets like the entorhinal cortex (EC).

Concurrent (online) TMS-fMRI allows for the real-time visualization of these effective connectivity patterns. Despite its promise, this method faces severe technical hurdles: the TMS coil and MRI receiver array compete for limited space, and TMS pulses induce transient B_0 field distortions (eddy currents) that degrade image quality. This work proposes a custom MRI receive coil mounted directly onto the TMS probe to recover SNR at the stimulation site while maintaining whole-brain coverage for concurrent spTMS-fMRI acquisition.

The probe-integrated receive coil addresses the geometric incompatibility that constrains concurrent TMS-fMRI to single-channel acquisitions. Improving tSNR at the stimulation site is expected to increase sensitivity to TMS-evoked BOLD responses, which are characteristically small in amplitude relative to background neural activity. This has downstream implications for causal connectome mapping in clinical populations, including the identification of fronto-limbic circuit biomarkers in trauma-related psychopathology, where effective connectivity measures are essential to distinguish causal from correlational circuit dysfunction.

This project aims to provide a tool for the neuroscience community aiming to transform TMS from a correlational assumption to a causally verified intervention. By enabling clear visualization of downstream activation in targets like the entorhinal cortex, this work supports the development of personalized, network-based treatments for neurodegenerative disorders.

Poster #33

Diffusion and Perfusion MRI-Linac Imaging to Optimise Radiation Treatment Volumes in Glioblastoma

Katelin Fung (Supervisor: Angus Lau)

Introduction. Glioblastoma (GBM) is an aggressive brain tumour with median survival of only 12-15 months. The standard-of-care treatment includes surgery, chemotherapy, and radiotherapy1. Because GBM tumours are infiltrative, there is microscopic tumour surrounding the gross tumour that is not visible on standard magnetic resonance imaging (MRI). To account for this microscopic spread, radiation is delivered to a 15 mm region surrounding the MRI-visible tumour. Yet, uniform expansion may not maximise tumour control while minimising side effects because 1) there is intratumoural heterogeneity and 2) irradiation is linked to side-effects such as lymphopenia (immunosuppression) which affects survival and quality of life.

MRI-Linacs are new machines that combine an MRI scanner with a linear accelerator for radiation delivery. MRI-Linacs allow radiation plans to be updated based on tumour changes visualised with MRI. Despite the potential for adaptive radiotherapy, current MRI techniques lack the ability to identify which regions should be treated and recurrence occurs in most patients. Determining which treatment regions to maximise tumour control and minimise side effects has not been well established. Diffusion- and perfusion-weighted imaging on conventional MRI could be predictive of geographical recurrence; however, this has not been validated on an MRI-Linac.

Diffusion and perfusion imaging can be accurately quantified with the MRI-Linac using apparent diffusion coefficient (ADC) and arterial spin labelling (ASL) respectively.

In tumours responding to treatment, there appears to be a greater change in diffusivity during treatment. In addition, tumours have increased perfusion compared to healthy tissue.

At Sunnybrook, there is a series of weekly adaptive radiotherapy trials (UNITED) for GBM patients aiming to access smaller margins and different dose schedules.

This study will reproduce these results with MRI-Linac imaging for integration into the adaptive radiotherapy workflow.

Methods. Between April 2021 and May 2023, 98 patients were treated with small-margin adaptive radiotherapy. Another 70 patients will receive small margin radiotherapy in the current trial (UNITED-3). Including patients on the UNITED trial, there is DWI imaging for 286 patients and ASL imaging for 135 patients. DWI imaging is processed to form ADC maps, allowing for changes in low-ADC tumour volume to be quantified. T1 weighted imaging and FLAIR imaging was collected every fraction, DWI imaging was collected 24 times, and ASL was collected more than 4 times in 32 patients.

Imaging data from GBM patients with different radiotherapy strategies will be compared to evaluate links between diffusion, perfusion, and recurrence. Past analyses of patients receiving conventional radiotherapy will be reproduced for patients receiving adaptive radiotherapy.

Results. Changes in diffusion were tracked in patients receiving standard-of-care treatment on MRI Linac in 17 patients.

Conclusion & Discussion. This work will evaluate if diffusion and perfusion are predictive of recurrence in MRI-Linac imaging. Using ADC and ASL could reduce the overall volume of irradiated tissue with more personalised treatment plans, reducing radiation side effects such as lymphopenia. Developing techniques to predict regions of recurrence using ADC and ASL could guide future treatments by targeting high-risk regions to delay progression.

Poster #34

Predicting Hepatic Arterial Infusion Pump Chemotherapy Outcomes from Radiology Images

Muhammad Alberb (Supervisor: Anne Martel)

Introduction. Colorectal cancer is the second leading cause of cancer-related death. The liver is the predominant site of colorectal cancer metastasis, substantially worsening patient outcomes. Hepatectomy is potentially curative for colorectal liver metastasis (CRLM). However, many metastases are initially unresectable. Hepatic arterial infusion pump (HAIP) is an implantable pump that delivers chemotherapy directly to the liver, concentrating cytotoxic agents within the hepatic circulation to shrink tumors and enable resectability. However, treatment response is highly variable, and predicting which patients will benefit from HAIP remains an unresolved challenge, as current prognostic biomarkers lack sufficient predictive power. Alternatively, radiological images routinely acquired for CRLM patients can be leveraged to extract quantitative features known as radiomics, which capture details beyond what is visible to the human eye. Coupled with machine learning, radiomics can enable predictive modeling for clinical decision-making, including diagnosis, prognosis, and treatment response prediction. Therefore, we hypothesize that pre-treatment CT-derived radiomics can predict HAIP outcomes.

Methods. We developed an automated radiomics pipeline for CRLM outcome prediction, comprising a segmentation model followed by a radiomics model. Using our annotation-efficient framework, the segmentation model was trained on an independent cohort to segment liver, spleen, vessels, and tumors. The model was then evaluated on a HAIP cohort and compared to inter-rater agreement rate. Afterwards, segmentations were used to extract per-region radiomic features, including morphology, texture, and intensity. Additionally, we extracted clinically relevant relative features, including tumor-liver volume, tumor-liver enhancement, tumor-vessel proximity, and liver-spleen attenuation. Using these features, we modeled conversion to resectability after HAIP using a multiple instance classifier. Specifically, our classifier consists of a tumor-level network that predicts per-tumor risk, followed by a pooling layer that computes patient-level probability of qualifying for surgery. To focus on high-risk tumors, the pooling layer leverages a smooth minimum operation to emphasize metastases with lower probabilities.

Results. Our segmentation model was trained on a public liver tumor dataset. Therefore, we evaluate its CRLM segmentation performance on a HAIP sample of 20 patients annotated by two independent experts. Our model achieved tumor segmentation Dice scores of 65% and 70% and detection F1-scores of 71% and 66% compared with the first and second annotators, respectively. Remarkably, the two annotators had mutual dice and F1 scores of 74% and 77%, respectively. After extracting radiomics using predicted segmentations, we train and evaluate our classifier on a cohort of 107 patients using repeated 3-fold cross-validation. The classifier achieves an area under the receiver operating characteristic curve (AUROC) of 73% and a balanced accuracy of 69% averaged over 100 repetitions.

Discussion and Conclusion. Our results demonstrate the potential of CT-derived radiomics to predict HAIP outcomes in patients with colorectal liver metastases. These findings highlight the promise of automated imaging biomarkers to support treatment planning and identify patients most likely to benefit from HAIP. Future work will focus on improving the predictive performance of the radiomics signature and extending the pipeline to predict additional endpoints, including chemotherapy toxicity, survival, and recurrence after surgery. Incorporating interpretability methods will also be essential to identify imaging features most strongly associated with outcomes.

Poster #35

Medical Image Synthesis for Optimizing the Diagnosis to Treatment Pathway in Radiation Oncology

Sophia Lollino (Supervisor: Thomas Purdie)

Introduction. Radiation therapy (RT) is an important component of cancer care, used in the treatment of approximately half of all cancer patients. The conventional RT treatment planning process involves acquiring additional images of the patient for preparation of the proposed RT treatment that will be delivered to the patient. Acquiring the RT specific imaging increases resource strain is a source of delay between cancer diagnosis and the start of RT, often by several days to weeks. Delays in treatment initiation have been associated with worse patient outcomes.

The objective of this project is to build an image-to-image machine learning (ML) model that generates synthetic RT planning computed tomography (CT) images from diagnostic CT images. The hypothesis is that ML will improve utilization of already available diagnostic CT imaging and eliminate the redundant imaging session for the RT treatment planning process. This will be tested by achieving the following aims: 1. Build and evaluate the technical performance of an ML model for generating RT planning CT images from readily available diagnostic images. 2. Evaluate automated image segmentation and dose prediction on the synthetic RT planning images against real RT planning images.

Methods. Aim 1: A dataset of paired 3D diagnostic and RT planning CT images from approximately 80 prostate cancer patients was split into a 70% training, 10% validation, and 20% testing split. We employed image-to-image translation methods based on Generative Adversarial Networks (GANs) to generate synthetic RT planning CTs from diagnostic CTs. Two GAN architectures, CycleGAN and a conditional GAN incorporating spatially adaptive normalization, have been implemented. The fidelity of the generated synthetic RT planning CTs was quantitatively assessed against the ground-truth RT planning CTs using Peak Signal-to-Noise Ratio (PSNR), Structural Similarity Index Measure (SSIM), and Mean Absolute Error (MAE). Aim 2: The synthetic images generated by the ML models will be assessed for clinical tasks like image segmentation and dose prediction for RT treatment planning. An automated segmentation method will be used to compare target and organ segmentations on the synthetic images and ground truth conventional CT images. For dosimetric validation, RT dose will be predicted on synthetic and conventional RT planning CTs.

Results. The CycleGAN model achieved an average PSNR of 20.21 dB ± 0.61 and SSIM of 0.65 ± 0.03, while the conditional GAN improved performance with an average PSNR of 25.86 dB ± 0.88 and SSIM of 0.77 ± 0.03, indicating closer similarity to the ground truth RT planning CT images. Future evaluation will involve assessing the synthetic images for clinical tasks like automated segmentation and dose prediction for RT treatment planning.

Conclusion. Our findings establish a ML pipeline for diagnostic CT to RT planning CT synthesis. By incorporating spatial priors, the conditional GAN model achieves improved fidelity over CycleGAN. This approach eliminates the need for redundant RT planning scans, accelerating treatment start dates, optimizing clinical resource utilization, and decreasing the number of hospital visits required before starting RT without any new hardware or major clinical infrastructure changes.

Poster #36

Self-Supervised Fuzzy Contrastive Learningfor Cervical Cancer Brachytherapy

Ryan Yan (Supervisor: Alexandra Rink)

Introduction. Many cervical cancer patients require radiotherapy for disease management, including high dose-rate brachytherapy (HDR BT), which involves inserting a radioactive source into the patient's body. HDR BT involves many imaging-based tasks performed manually by a human, which are time consuming, requiring the patient to remain on the treatment bed for 3 hours. Reducing treatment time has been shown to reduce side effects of HDR BT, motivating the automation of these manual tasks. Supervised learning approaches havebeen proposed and implemented, but requiredata with labels created manually by trained clinical team members, which is limited in availability.This project aims to use self-supervised learning, requiring no labels, to train a model on an internal dataset of CT and MRI images.

Methods. Since the dataset has multiple imaging modalities, contrastive learning (CL) can be applied, in which the model learns to associate scans from the same patient. While each modality has unique information, scans of the same patient have consistent anatomical structures and disease extent across them. We introduce a fuzzy CL method, using structural similarity and clinical staging to measure the similarity between scans of different patients. This metric is used to encourage the model to also learn associationsbetween highly similar patients. The proposed fuzzy CL was used to train a vision transformer (ViT) modelon a dataset of 15 patients (75 MRIand15 CTscans) from a baseline model pretrained on CT data. The trained ViT was adapted to a segmentation model, then fine-tuned on a labeled MRI dataset for organ-at-risk (OAR) and high-risk clinical target volume (HR-CTV) contouring, which is a manual task in HDR BT. This dataset had 76 patients and 128 MRI scans.

Results. The model outputswere evaluated using the Dice score, a measure of overlap between the prediction and ground truth. The fuzzy CL method resulted in a significant increase in performance on HR-CTV (Dice = 0.58) compared to the baseline ViT (Dice = 0.51) and a U-Net segmentation model trained from scratch (Dice = 0.42). For OAR segmentation, the fuzzy CL achieved comparable results to the baseline ViT and U-Net, but did not significantly outperform both modelson anytarget (bladder, rectum, sigmoid, or small bowel).

Discussion. The HR-CTV includes regions of concern for disease that may not be readily apparent through imaging alone, so clinical information is typically used to delineate this region6. The fuzzy CL method incorporates some clinical information into the training process, encouraging the model to learn image features relevantto disease extent,potentially explaining the improvement in HR-CTVsegmentation performance.

Conclusion. A fuzzy contrastive loss was used for self-supervised pretraining of a ViT for cervical cancer, with initial promising results. Future experiments will scale this method to a larger dataset including cone-beam CT and PET scans, along with additional tuning of training parameters and the similarity metric.

Poster #37

Integrating Bloodwork into Multi-Modal Clinical Decision-Making

Gerd Bizi (Supervisor: Chris McIntosh)

Physicians integrate heterogeneous data like imaging, physiological signals, and laboratory results to inform clinical decisions, yet medical AI systems remain largely limited to single-modality or paired-modality analysis. The McIntosh Lab's ProbMED framework addresses this by embedding clinical reports, chest X-rays (CXR), electrocardiograms (ECG), and echocardiograms (ECHO) in a shared representational space through contrastive learning, enabling cross-modal retrieval across a patient's full clinical picture. Despite its diagnostic value, routine bloodwork has not yet been incorporated into this framework.

Integrating bloodwork into ProbMED opens the door to opportunistic screening as bloodwork is a common component of routine care. Consider a patient presenting for an annual checkup with concerns about recurring fatigue. Their physician orders a complete metabolic panel with iron studies. The iron levels return normal, but the panel reveals low albumin, a subtly elevated BUN-to-creatinine ratio, and borderline hyponatremia. Each finding is individually unremarkable, but together, these signals co-occurred with reduced ejection fraction, a condition normally diagnosed using ECHO. Using our model, this patient's bloodwork could be queried and the ECHO-level diagnosis could be suggested. What began as routine bloodwork now carries an actionable signal for specialized follow-up, catching a condition the patient never suspected.

Using the MIMIC-IV database (~300K patients with paired CXRs, ECGs, ECHOs, and bloodwork), I propose augmenting ProbMED with bloodwork embeddings derived from a tabular foundation model (TabICLv2), aligned contrastively with existing modalities. Preliminary work using a supervised random forest achieved an AUROC of 0.70 predicting CXR diagnoses from a 30-feature blood panel, establishing that routine bloodwork carries meaningful cross-modal signal. Additionally, fine-tuning a pre-trained DenseNet, a type of neural network for images, to predict abnormal bloodwork also achieved an AUROC of 0.66, indicating bi-directional cross-modality between CXR and bloodwork.

This work would be the first integration of bloodwork into a contrastive multimodal clinical AI framework, with the potential to accelerate diagnosis in settings like the emergency room or to open the doors to opportunistic screenings, leveraging easier-to-acquire modalities to derive insights from more specialized ones.

Poster #38

Child Brain Imaging Outcomes Following the VID-KIDS Program for Improving Interactions Between Depressed Mothers and their Infants

Grace Burns (Supervisor: Kathryn Manning)

Introduction. Postpartum depression affects an estimated 12-15% of mothers globally and is associated with reduced mother-infant interaction quality and altered child development. The VID-KIDS program is a nurse-delivered video-feedback intervention designed to enhance 'serve and return' interactions by improving depressed mothers' sensitivity and responsiveness to infant cues. Characterizing how maternal depression shapes the developing brain, and whether early supportive interventions, like VID-KIDS, can meaningfully alter developmental trajectories, is crucial for improving long-term outcomes for families. Evidence from electroencephalogram (EEG) studies links right-frontal asymmetry, a marker associated with depression, to children exposed to maternal depression, and positive mother-infant interactions have been shown to mitigate this asymmetry. However, MRI-based investigations of how parenting interventions may shape developing neural circuits remain limited.

Methods. The VID-KIDS randomized controlled trial enrolled 140 mother-infant dyads (75 intervention, 65 control) (5). Interaction quality (Parent-Child Interaction Teaching Scale), maternal depressive symptoms (EPDS), and child developmental outcomes (ASQ-3) were assessed at baseline, immediately post-intervention, and at a two-month follow-up. A neuroimaging subset followed up on 48 children between ages 3 and 8 (31 intervention, 17 control, 30 male, mean age = 4.9 years). Child behavioural outcomes at the MRI timepoint were assessed using the Child Behaviour Checklist (CBCL) and the Behavior Rating Inventory of Executive Function - Preschool Version (BRIEF-P). Resting-state functional MRI (fMRI) and diffusion tensor imaging (DTI) data will be preprocessed using FSL software. The frontal-parietal functional network will be uncovered using independent component analysis, and nodes will serve as seeds for diffusion tractography. Imaging and survey data of children whose mothers received the VID-KIDS treatment willbe compared to those of children whose mothers did not. To further uncover the mitigating effects of this intervention, the treated group will also be compared to age-matched participants in the Pregnancy during the Pandemic study (6) who were not exposed to maternal depression.

Results. Significantly higher mother-child interaction scores were observed in the intervention group compared to the control, both immediately post-test and 2 months post-intervention. Images from 36 (23 intervention, 13 control, 23 male, mean age = 5.3 years) participants were successfully collected. The control group will be supplemented with children matching the VID-KIDS inclusion criteria from the Pregnancy during the Pandemic Study. Group differences in the functional and structural connectivity and lateralization of the frontal-parietal network. Linear mixed-effects models will be used to determine relationships between maternal symptoms, child behaviour, and brain connectivity.

Conclusion. VID-KIDS improves early mother-infant interaction quality among mothers experiencing postpartum depression. We will integrate behavioral outcomes of mothers and children with functional and diffusion-based MRI findings to explore how early interventions influence the organization and development of child brain network connectivity.

Poster #39

Effects of Maternal Physical Activity on the Neurodevelopment of Progeny

Alena Ionova (Supervisor: Kathryn Manning)

Introduction. During pregnancy there is a dramatic formation of neurons in the fetal brain and compromised maternal health may disrupt this process. While physical activity (PA) has broad benefits, little is known about the specific impact of PA during pregnancy upon the developing child. In animal models, prenatal PA (pPA) reduces offspring anxiety, increases neurotrophic factors, and buffers consequences of prenatal stress. In humans, pPA has been associated with increased child IQ and cerebral maturation, though findings are mixed. Accelerometer-measured pPA was associated with increased infant cortical thickness, but not hippocampal volume in older children, as measured via Magnetic Resonance Imaging (MRI). The hippocampus is particularly sensitive to changes in the internal environment, making it a focal region for investigation. Yet, the longitudinal effects of pPA on child behaviour and early brain development, and its potential to mitigate prenatal stress, remain unclear.

Objective and Hypothesis. This study examines if pPA is associated with (a) maternal outcomes and (b) offspring neurodevelopment, with focus on hippocampal structure and connectivity in infancy, and (c) to determine whether pPA can mediate the impacts of prenatal stress. We hypothesize that higher pPA levels will correlate with improved maternal mental health and sleep duration, better child development scores, and more mature hippocampal structure and connectivity.

Methods. Data from the Pregnancy during the Pandemic study was used, with minutes of moderate-to-strenuous pPA (Godin-Shephard Leisure-Time Exercise Questionnaire; GLTEQ) as the main predictor. Maternal data, excluding those with substance use (n>8,000), included measures of mental health (Edinburgh Postnatal Depression Scale; EPDS, Patient-Reported Outcomes Measurement Information System (PROMIS) anxiety), sleep duration, and delivery outcomes, was analyzed with mixed-effects models, while controlling for household income. Child development was assessed via sleep (Brief Infant Sleep Questionnaire; BISQ), infant behaviour (Infant Behaviour Questionnaire; IBQ), and milestones (Ages and Stages; ASQ), with linear models evaluating associations with pPA. A subset of children (n=109) had MRI scans acquired at 3 months of age on a 3T scanner at the Alberta Children's Hospital. FSL software will be used to quantify the volume of the hippocampus, as well as its structural and functional connectivity with hubs of the limbic network. Following standard preprocessing, data will undergo segmentation, tractography, and connectivity analyses. Group differences by pPA levels will be assessed using general linear models with multiple-comparison correction, followed by mediation analyses to assess whether pPA attenuates the effects of prenatal stress on child outcomes.

Results. Of the larger maternal cohort (mean age = 31.8±4.4 years), 34.1% met physical activity guidelines of 150 minutes of moderate activity per week, at intake. Preliminary results on the effects of minutes of pPA per week on maternal sleep length suggest that while pPA had a small negative correlation with sleep (β=-0.05, SE=0.019, p=0.0057), higher mental health symptoms and parity emerged as strong negative predictors.

Conclusion. This project investigates the effects of pPA which has the potential to support the development of future health policies and interventions.

Poster #40

Multimodal Image Analysis of Cerebral Arterial Morphology Using Deep Learning-Based Semantic Segmentation

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Introduction. Angiography imaging is key to visualizing vascular abnormalities and diagnosing cerebrovascular conditions such as intracranial aneurysms (IA), which can occur when an artery abnormally outpouches, risking rupture and subsequent hemorrhage surrounding the brain. Among the most common angiography approaches to visualize IA, Computed Tomography Angiography (CTA) using an iodine-based contrast agent is more clinically prevalent than Time of Flight MR Angiography (TOF-MRA) due to its greater accessibility. Visual and quantitative characterization of vessel morphology, including branching patterns, bifurcation angles, and vessel length, can inform growth and rupture risk of IA.

Recent studies interested in the cerebral vasculature have deployed multi-label semantic segmentation tools showcasing the potential for deep learning models to segment the circle of Willis (CoW) with accurate accuracy. Although the CoW is key to maintaining perfusion across the brain, it represents only a small proportion of the clinically relevant arterial anatomy, such as aneurysms and other vascular abnormalities that may be just a few centimeters downstream of the CoW and reflecting the vastness of arterial morphology yet to be uncovered. Understanding the brain's vasculature in greater detail with high sensitivity and specificity, can lead to more precise treatment planning and provide additional diagnostic information during time-critical situations such as ruptured IAs.

Hypothesis. We hypothesize that semantic segmentation will achieve sensitivity and specificity ($\geqslant$90%) as it relates to major arterial branches.

Aims and Experimental Approach.

1. Establish semantic segmentation of major cerebral arteries and their branches in both CTA and TOF-MRA images using deep-learning based approaches. a. Create binary segmentation of vessels in CTA and TOF-MRA. b. Create precise multi-label annotations of the major arteries beyond the CoW and their branches. c. Validate annotations with clinician experts using clinical samples of IA.
2. Enhance the model's specificity in detecting small vessels to support clinical diagnosis of IA. a. Collect 7 Tesla TOF-MRA data from ~30 healthy participants to serve as ground truth of typical segmentation of arteries deeper in the vascular network. b. Quantify morphological parameters to identify deviations from typical arterial anatomy to inform detection of IA. c. Identify segmentation performance using Dice Similarity Coefficient (DSC).

Conclusion: By developing a multi-label semantic segmentation model leveraging both CTA and TOF-MRA, we expect to achieve high sensitivity and specificity in identifying major cerebral arterial structures, ultimately supporting improved detection and morphological characterization of IA. Ultimately, improved mapping of cerebral arterial morphology has the potential to reduce diagnostic uncertainty in IA management, supporting earlier intervention and better patient outcomes.

Poster #41

Investigating Cellular Glucose Metabolism in a Transgenic Mouse Model of Chronic Stress

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The human brain is the body's central command center, continuously integrating and processing internal and external information to maintain physiological function and coordinate behavior. Its fundamental cellular units are neurons. To support normal neuronal function, the brain requires substantial energy to maintain normal physiology. Glucose is the brain's primary energy source. Tight regulation of glucose metabolism by neurons and glial cells is critical for brain physiology, and disruptions in this process underlie several diseases. However, the precise cellular contributions to overall glucose utilization have remained controversial for decades, largely because most technologies to date lacked the spatiotemporal resolution required to quantify metabolic activity in single cells in situ.

When stress exceeds the body's natural regulatory capacity, or homeostasis, the body adapts to restore homeostasis and promote survival. Stress-induced glucocorticoids serve several functions, including mobilizing energy stores and increasing blood glucose levels to ensure adequate energy supply during the stress response. While glucocorticoids are essential for acute stress responses, chronic stress leads to prolonged exposure to elevated glucocorticoids and imbalances in glucose metabolism, contributing to stress-related pathophysiology, such as chronic inflammation, neurodegeneration, and pathological aging. However, how neuroenergetics is altered in response to stress remains largely unknown. Direct measurement of cellular-level changes in situ remains limited, largely due to the lack of suitable models and tools.

To investigate cellular changes and cell-cell interactions during neuroenergetics under chronic stress, the following research question is proposed: **How are neuronal and glial glucose metabolism, and glial-neuronal interactions, altered by chronic stress?** To address this, the following aim will be pursued: Compare metabolic alterations in neurons, and astrocytes across hippocampus, hypothalamus and prefrontal cortex under stress-free and chronically stressed conditions. In situ metabolic imaging of redox states between stress-free and chronically stressed experimental groups will be compared. Specifically, **C57BL6/N male and female mice with transgenic Peredox sensors** will be randomly assigned into two groups: a control group, and an experimental group administered with 8 weeks of stressors. The stress induction procedure will follow the **unpredictable chronic mild stress (UCMS) paradigm**. At the beginning and the end of the UCMS paradigm, **behavioral tests** will be conducted to assess cognitive states. Then **acute brain slices** will be sampled to maintain physiological dynamics of brain cells, and imaged to assess cell glucose metabolism. Peredox sensors in neurons and astrocytes will be activated to detect cytosolic NADH and NAD+ and inform cellular redox states. **Fluorescence decay signals** from the Peredox sensors will be detected by **two-photon fluorescence lifetime imaging microscopy (2P-FLIM)**. Anticipated results of the chronically stressed mice will likely include longer lifetime in both neurons and astrocytes, which indicates a higher NADH:NAD+ ratio, increased glycolysis, and glucose hypometabolism. Depression-like behaviors will be identified in this group. The control group will show oxidative states in neurons (indicated by short lifetime and lower NADH:HAD+ ratio) and glycolytic states in astrocytes (indicated by long lifetime and higher NADH:NAD+ ratio), accompanied by healthy behaviors.