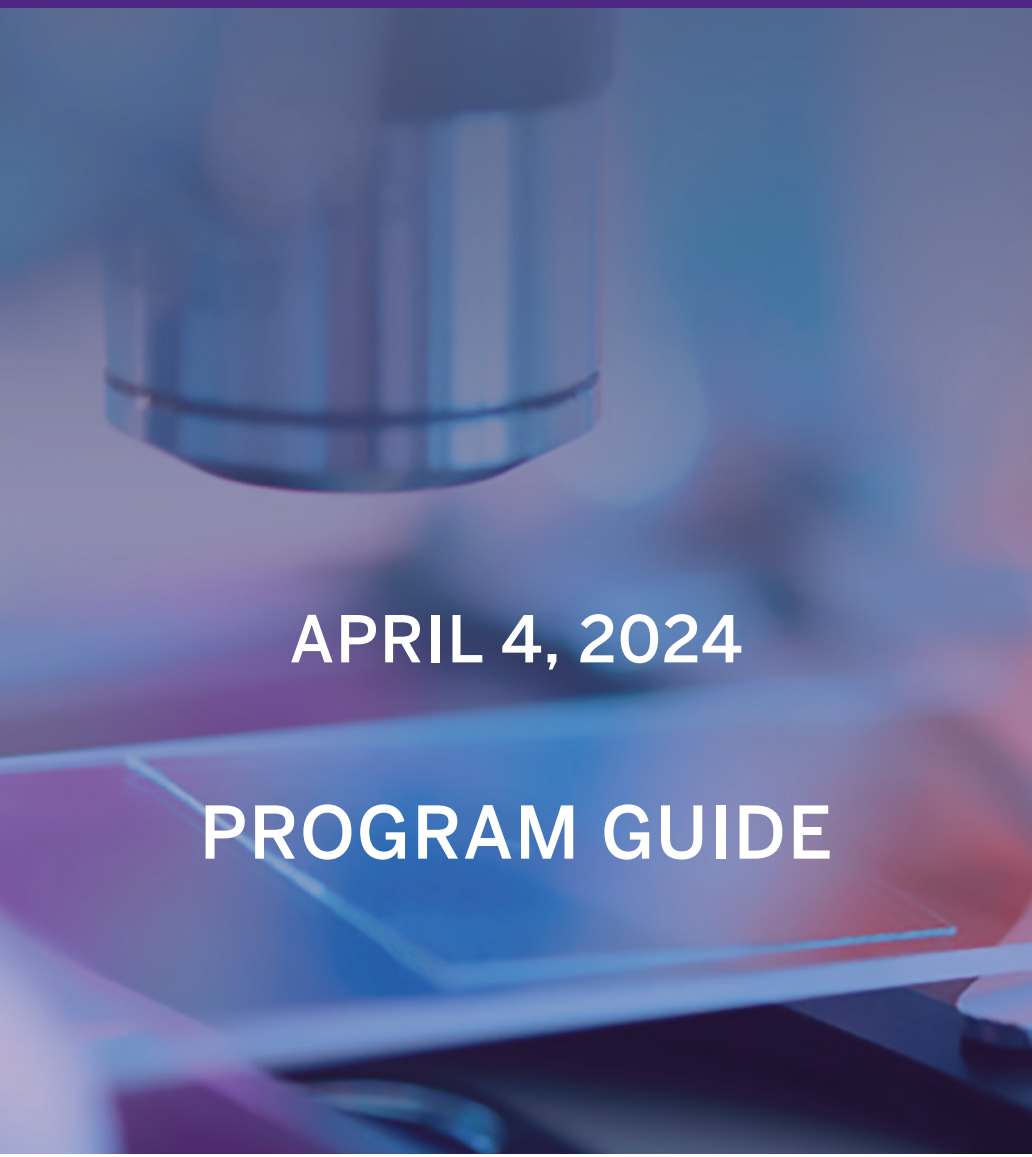
PATHOLOGY AND LABORATORY MEDICINE

RESEARCH DAY 2024



APRIL 4, 2024

PROGRAM GUIDE

Schulich MEDICINE & DENTISTRY

London Health Sciences Centre

Western

Welcome to one of our department's most important academic events of the year. Our Pathology and Laboratory Medicine Research Day showcases our research accomplishments, celebrates our people, and gives us a glimpse into an exciting future for both our department, as well as for our School and University.

This year, we have 107 research presentations, given by an array of researchers that display the breadth of our department's research. Most presenters are undergraduate students, graduate students, and residents; the research being presented spans all of our department's research themes, including amongst others, cancer biology, cardiovascular, respiratory and metabolic diseases, infection, immunity and inflammation, bioinformatics and data science, and digital pathology.

This year, we welcome Dr. Michael Laflamme who is a Professor in the Department of Laboratory Medicine & Pathobiology at the University of Toronto and a Staff Pathologist in the University Health Network Laboratory Medicine Program, practicing diagnostic cardiovascular and autopsy pathology. Dr. Laflamme holds the Robert McEwen Chair in Cardiac Regenerative Medicine and the Tier 1 Canada Research Chair in Cardiovascular Regenerative Medicine. His research program is aimed at developing novel cell therapies to regenerate injured hearts.
The organizing committee and many members of our department have dedicated considerable time to ensure that this day is a rewarding experience for our department members and for our wider community. I would like to thank the Research Day Committee as well as the members of our university department staff for their tremendous work in putting this day together, and my thanks to all of the judges for their invaluable service. My heartfelt congratulations to all of the presenters for the work that you have done on your research and for representing the Department of Pathology and Laboratory Medicine. And finally, I would like to thank all of you for attending and supporting our department. I hope that you enjoy our multi-disciplinary approach to studying health and disease, as you listen to the platform presentations and view the posters.

David Driman, MBChB, FRCPC
Professor and Chair,
Schulich School of Medicine & Dentistry, Western University
Department Head, London Health Sciences Centre
Chief, St. Joseph's Health Care London
Department of Pathology and Laboratory Medicinee

Michael Laflamme, MD, PhD

Robert McEwen Chair in Cardiac Regenerative Medicine
Canada Research Chair, Cardiovascular Regenerative Medicine
Senior Scientist, McEwen Stem Cell Institute
Staff Pathologist, UHN Laboratory Medicine Program
Professor, Laboratory Medicine and Pathobiology,
University of Toronto

"Heart Regeneration with Human Pluripotent Stem Cells"

3:15 p.m. – 4:20 p.m.

9:00 – 9:10 a.m.	**Welcome and Opening Remarks** **Dr. David Driman** Chair/Department Head, Pathology and Laboratory Medicine, Schulich Medicine & Dentistry, Western University and London Health Sciences Centre
9:15 – 10:30 a.m.	**Poster Presentations – Session 1**
10:30 – 10:45 a.m.	Nutritional Break
10:45 – 12:00 p.m.	**Poster Presentations – Session 2**
12:00 – 12:50 p.m.	Lunch
1:00 – 2:00 p.m.	**Platform Presentations – Session 1**
2:00 – 2:15 p.m.	Nutritional Break
2:15 – 3:00 p.m.	**Platform Presentations – Session 2**
3:00 – 3:15 p.m.	Nutritional Break
3:15 – 4:20 p.m.	**Keynote** **Dr. Michael Laflamme** Robert McEwen Chair in Cardiac Regenerative Medicine; Professor, Laboratory Medicine and Pathobiology, University of Toronto
4:20 – 4:30 p.m.	Group Photo
4:30 – 5:00 p.m.	**Research Day Award Presentation**

Poster Presentations
Session 1
9:15 a.m. - 10:30 a.m.

#	First Name	Last Name	Title
1	Victoria	Chharawala	A Geographical Needs Analysis of Ophthalmologists in Ontario: Current Assessment of Specialist Distribution and Patient Demand
2	Sabina	Al Agbar	Impact of Non-HLA Antibodies on Delayed Graft Function, Rejection, and Graft Survival in Kidney Transplantation
3	Eric	Wang	Heterogenic endothelial dysfunction in target organs of chronic diabetic complications, regulation by miR-9
4	David	Weng	Synthetic lethality and single-cell transcriptomic signature driven drug repurposing for ER+/HER2+ breast cancer
5	Amaan	Bari	Phytocannabinoid-induced Reprogramming of Mouse αTC1-6 cells
6	Rachel	Barboza	The Molecular Characteristics of Granular Mitosis in Glioblastomas
7	Samantha	Lim	Comparative Analysis of ChatGPT 4.0 and Pathologists' Assistants in Generating Gross Descriptions of Surgical Specimens
8	Carolyn	Lauzon-Young	Defining Epigenomic DNA Methylation Biomarkers in Myeloid Malignancies
9	Danielle	Taray-Matheson	The role of circHUWE1 in prostate cancer

#	First Name	Last Name	Title
10	Hasti	Gholami	The impact of gut microbiota on the response to immune checkpoint blockade in neuroblastoma tumours induced to be immunologically active
11	Cody	Hird	Developing Chimeric Coronavirus Spike Proteins as Universal Vaccine Candidates
12	Gracie	Sun	The LinkUp Study – Evaluating the Outcomes of the 519Pursuit's LinkUp Mentorship Program & the Role of Mentorship in Social Inclusion for People Experiencing Homelessness in London, Ontario
13	Maya	Resendes Torrado	Assessing Hyperglycemic Memory Duration via ECM Gene Expression
14	Sumaiyah	Wasif	Investigating the Role of Netrin Signalling in High-Grade Serous Ovarian Cancer
15	Shreya	Sharma	Investigation of the Environmental Impacts of the Cryptocurrency Industry
16	Elly	Shin	Elucidating the Mechanism(s) of Mito-Nuclear Crosstalk
17	Grace Eunbin	Kim	In vitro modeling of the Hematopoietic Stem Cell Niche using CD133+ stem cell overlay culture system
18	Maya	Potter	Early detection of SARS-CoV-2 variants of concern using a wastewater surveillance model

#	First Name	Last Name	Title
19	Juhi	Mattekatt	Investigation of Antimicrobial Stewardship in North American Indigenous Communities
20	Brandon	Brower	Investigating the Recent Rise in Peritoneal Mesothelioma Cases in London and Area
21	Esther	Chang	The Impact of Bone Morphogenic Protein on SATB2-Mediated Heterotopic Gingival Ossification
22	Derick	Liang	Application of Machine Learning in Predicting Gene Expression Profiles of Individual Cells Using Their Chromatin Accessibility Activities
23	Nachuan Harrison	Pan	The Therapeutic Potential of Naporafenib in Anaplastic Thyroid Carcinoma
24	Mohammad Hossein	Derakhshan Nazari	Data Integration to Uncover Cell Type-Specific Regulatory Mechanisms Driving Risk to Inflammatory Bowel Disease
25	Michael	Tran	Investigating the role of surface-exposed proteins in virus evolution
26	Laura	Lockau	A case of post-transplant progression in a cardiac allograft with pre-existing transthyretin amyloidosis
27	Bernardo	Reyes-Ballesteros	Would SARS-CoV-2 be able to infect mammals relevant to Aotearoa New Zealand?

#	First Name	Last Name	Title
28	Luis	Limo	Unraveling the Influence of the Exposome on the Human Oral Microbiome: A Scoping Review in the One Health Approach
29	Cole	Harris	The Role of miR-9 in Alzheimer's Disease
30	Felobater	Halka	S100A7 Levels as a Marker for Predicting Malignant Transformation in Actinic Cheilitis
31	William	McCullagh	Regulation of danger signalling in proximal tubule epithelial cells
32	Adam	Greasley	Circular RNA HIPK3 Regulates Mitochondrial Apoptosis through Binding to ACAD9 and Ndufv1
33	Seungwon	Han	Tuberculosis in an Urbanizing Kenya: Investigating the link between urbanization in the 21st century and human, bovine, and zoonotic tuberculosis
34	Natalie	Grindrod	The digital pathology of TILs as a biomarker in breast cancer
35	Nader	Hosseini Naghavi	Integrative Data Analysis to Uncover Transcription Factors Involved in Gene Dysregulation of Nine Autoimmune and Inflammatory Diseases
36	Frederikke	Larsen	Activation of a viral mimicry response inhibits colitis-associated cancer

#	First Name	Last Name	Title
37	R. Leigh	Hamel-Smith Grassby	Juvenile mucoepidermoid carcinoma of the lung with p40 negativity
38	Judy	Wang	Investigating electrocardiographic abnormalities as predictors for Post-Stroke Major Adverse Cardiovascular Events
39	Cornelius	Osei-Owusu	Microcirculation and Critical Limb Ischemia
40	Sewon	Kim	The utility of p16 and p53 immunohistochemistry staining to determine the prevalence of HPV in Oropharyngeal squamous cell carcinomas submitted by Ontario dentists
41	Jacob A.	Houpt	Clear Cell Renal Cell Carcinoma with Hemangioblastoma-like Change in a Pediatric Patient with Tuberous Sclerosis Complex: the Morphological Intersection of Neuro- and Uro-pathology
42	Phyo	Win	Nuclear and mitochondrial DNA variation drive cardiovascular disease risk
43	Julia	Steriopoulos	The Molecular Mechanism of TLR3 Initiated Cell Death in Cardiac Allografts
44	Xinru	Li	Molecular Evaluation of Clinical Diagnosis of Oral Potential Malignant Disorders

#	First Name	Last Name	Title
45	Chao	Wang	Inhibition of histone deacetylases aggravates doxorubicin-induced injury in cardiomyocytes
46	Riya	Tangri	Genome-wide Meta-Analysis of the Human Placental Transcriptome in Association with Maternal Pre-pregnancy Body Mass Index
47	Urooj	Syed	Profiling bone marrow stem cell niche interactions in ageing
48	Alana	Lopes	Exploring the Non-Medical Application of Pathologists' Visual Search Skills
49	Charlotte	Hayes	Reasons for Submission of Placentas to Pathology: A Review with Diagnostic Correlation and Estimation of Clinical Impact
50	Patricia	Rudak	Development and Evaluation of a Novel Tile-based Digital Image Classification Application for Continuing Professional Development in Pathology

Presenter's Name: Chharawala, Victoria

Additional Author(s): Zhang R, Armstrong JJ, Hutnik CML

Abstract Title: A Geographical Needs Analysis of Ophthalmologists in Ontario: Current Assessment of Specialist Distribution and Patient Demand

Abstract:
Introduction: Ophthalmologists are few relative to the population of Ontario and tend to practice in large population centres with secondary and tertiary care hospitals. More broadly, Ontario's population is growing and aging, placing additional demands on the short supply of ophthalmologists. The purpose of this study is to determine the geographic distribution of practicing ophthalmologists in relation to patients seeking ophthalmologic care in Ontario. It is hypothesized that differences in geographic distributions of patients and ophthalmologists will be associated with health inequalities in access to specialized eye care services in Ontario. In addition, temporal trends in population-level characteristics, such as median age and population size, will confirm an increasing need for ophthalmologists in Ontario.

Methods: A retrospective analysis of ophthalmic service billing claims data from the Ontario Ministry of Health and Long-Term Care between January 2016 and October 2023 was performed. This included counts of service claims for each pair of physician and patient forward sortation areas (FSA), the nature of the service provided, and a patient age range. A similar retrospective analysis, between September 11th and September 30th, 2023, was undertaken utilizing ophthalmology patients' electronic health records from the Ivey Urgent Eye Clinic at St. Joseph's Hospital in London, Ontario. Here, data collection included patient postal code, diagnosis, date and time of visit, number of follow-ups, patient age, speciality of the referring physician, and the referring complaint. Population-level data for age, growth distributions, and FSA boundaries were obtained from the 2021 Canadian census. Altogether, patient and physician distributions, patient characteristics, and population characteristics were visualized using ArcGIS Online mapping software and analyzed statistically in R.

Results: Analyses to date suggest disparities between physician and patient distributions, which may contribute to longer distances travelled for patients to access ophthalmic care. Mapped temporal shifts in patient distributions appear to correlate with the aging and growing population of Ontario.

Discussion: Identifying unknown factors such as patient-to-physician distance, local specialist density, and areas in need of increased ophthalmologist supply in Ontario is key to improving healthcare accessibility and informing future human resource allocation in ophthalmology.

Research theme 1: Cardiovascular, Respiratory Health, and Metabolic Diseases
Research theme 2:
Research theme 3:

Presenter's Name: Al Agbar, Sabina

Additional Author(s): Raina N, Rocheleau K, Panecaldo V, De Koning K, de Chickera S, Gunaratnam L, Sidahmed A

Abstract Title: Impact of Non-HLA Antibodies on Delayed Graft Function, Rejection, and Graft Survival in Kidney Transplantation

Abstract:
Introduction: Kidney transplantation (KT) is the preferred treatment for end-stage kidney disease, offering improved quality of life and longer survival compared to dialysis. However, the success of KT is limited by the occurrence of organ rejection, often mediated by the immune system's response to mismatched human leukocyte antigen (HLA) molecules. Recent evidence suggests that non-HLA antibodies, exposed post-injury and less understood, might also contribute to KT failure, even in the absence of HLA donor-specific antibodies (DSAs). Delayed graft function (DGF) is defined as the requirement for dialysis within the first week post-transplant most often caused by ischemia-reperfusion injury to the grant. Consequently, non-HLA antibodies may be generated in the immediate post-operative period, potentially contributing to this phenomenon. This study aims to explore the impact of non-HLA antibodies on KT outcomes to enhance the understanding and management of kidney transplantation.

Methods: We will conduct a comprehensive retrospective analysis of 450 KT recipients from London Health Sciences Centre, categorized into three groups: 150 with biopsy-proven rejection, 150 with DGF, and 150 without these complications. We will utilize enzyme-linked immunosorbent assays (ELISA) and multiplex Luminex assays to test for 40 potential non-HLA antibodies pre- and post-transplant. This study aims to identify correlations between non-HLA antibodies and adverse KT outcomes, considering factors such as HLA mismatches and anti-HLA DSAs.

Results/Expected Outcomes: We anticipate finding a significant correlation between certain non-HLA antibodies and adverse KT outcomes, such as DGF and rejection. This could reveal a synergistic interaction between non-HLA antibodies and HLA DSAs, challenging current understandings of KT rejection mechanisms. Identifying specific non-HLA antibodies associated with poor outcomes may lead to the development of targeted treatments and improved monitoring practices, potentially extending the lifespan of transplanted kidneys.

Discussion: Understanding the role of non-HLA antibodies in KT rejection could revolutionize transplant medicine by offering new avenues for diagnosis, monitoring, and treatment. This research has the potential to significantly improve success rates and health outcomes for KT recipients, contributing to the advancement of transplantation medicine and offering hope to thousands of Canadians in need of kidney transplants.

Research theme 1: Infection, Immunity, and Inflammation
Research theme 2: Regenerative and Transplantation Medicine
Research theme 3:

Presenter's Name: Wang, Eric

Additional Author(s): Feng B, Chakrabarti S

Abstract Title: Heterogenic endothelial dysfunction in target organs of chronic diabetic complications, regulation by miR-9

Abstract:
Introduction: Diabetes and its complications reduce patients' qualities of life. Chronic diabetic complications begin with hyperglycemic damage to microvascular endothelial cells (MECs), leading to further dysfunction. Despite common origins, the manifestations of diabetic complications diverge as they progress. We hypothesized that transcriptomic differences in MECs contribute to the differences in disease manifestations across diabetic complications. Furthermore, because these MECs share a genomic sequence, differences in gene expression are attributable to differential epigenetic regulation. We hypothesized that there may be key epigenetic regulators of MEC dysfunction that act on MECs across different diabetic complications.

Methods: Nanostring DSP analysis was performed on early diabetic and age-matched non-diabetic C57BL/6 mice. Gene set enrichment analyses were performed on transcriptomic data from retinal, renal, and cardiac MECs. Changes in microRNA expressions were approximated by changes in microRNA targets. miR-9 was identified as a miRNA of interest and potential key regulator. Human retinal and cardiac MECs were cultured in normal (5mM) and high (25mM) glucose conditions to confirm the downregulation of miR-9. miR-9 levels were manipulated using mimics and antagomirs to assess its role in the glucose-induced endothelial responses of retinal and cardiac MECs. Endothelial-specific miR-9 overexpressing mice were generated and used to validate our findings in vivo.

Results: We found that MECs from the retina, kidneys, and heart were transcriptomically distinct, and that they have largely unique responses to hyperglycemic insult at an early stage of diabetes. Increased ECM production were common characteristics of the assessed MECs. miR-9 was confirmed to be downregulated in retinal and cardiac MECs. miR-9 inhibition was associated with a form of endothelial dysfunction known as endothelial-to-mesenchymal transition (EndMT), which promotes mesenchymal phenotypes in MECs and increases ECM protein production. miR-9 regulated EndMT both in vitro and in vivo in retinal and cardiac MECs.

Discussion: MECs from differing organs have unique transcriptomic profiles and largely unique responses to diabetes but have some similarities which are regulated through miR-9. miR-9 may represent an option for pan-complication treatment in diabetes.

Research theme 1: Cardiovascular, Respiratory Health, and Metabolic Diseases
Research theme 2: Epigenetics
Research theme 3: Cardiovascular, Respiratory Health, and Metabolic Diseases

Presenter's Name: Weng, David

Additional Author(s): Hu P

Abstract Title: Synthetic lethality and single-cell transcriptomic signature driven drug repurposing for ER+/HER2+ breast cancer

Abstract:
Background: Breast cancer heterogeneity poses challenges in determining effective treatment strategies. Current clinical subtyping based on receptors fails to fully capture the heterogeneity found in the disease. Highly heterogeneous subtypes — such as estrogen receptor positive and human epidermal growth factor receptor 2 positive (ER+/HER2+) breast cancers — show high variability in patient outcomes. Differences in gene expression have been used to delineate subgroups with worse prognoses within the ER+/HER2+ subtype using single-cell RNA sequencing (scRNA-seq). This technology can also identify synthetic lethality (SL), a genetic interaction where only simultaneous loss of function in both genes leads to cell death, uncovering targets for cancer-specific treatments. We aim to leverage scRNA-seq to identify potential repurposed drugs to target subgroups in ER+/HER2+ breast cancer through two avenues — SL and reversal of disease transcriptomic signatures.

Methodology: SL genes are uncovered using the tool Synthetic Lethal Identification in R (SLIdR) using viability scores predicted from DepMap and mutation data from cBioPortal across 1201 breast cancer patients in The Cancer Genome Atlas (TCGA) samples with oncogenes defined with COSMIC cancer gene census' Tier 1 breast cancer genes. Reversal of transcriptomic signature uses the tool A Single-cell Guided Pipeline to Aid Repurposing of Drugs (ASGARD) with a treated and untreated ER+/HER2+ breast cancer sample and three healthy references. ASGARD generates predicted repurposed drugs and SL genes are used as targets in DrugBank drug searches. Validation of repurposed drugs uses computational prediction of binding, literature review, and ADMET models.

Results: SLIdR analysis found two SL gene pairs sharing a driver gene — FOXA1-MUC16 and FOXA1-CHST11. Repurposed mono-drug and drug combinations will be identified by ASGARD. Drugs targeting MUC16 and CHST11 will be searched for using DrugBank. All potential drugs will be assessed using computational tools and literature review.

Discussion: We attempt to find potential therapeutic approaches for ER+/HER2+ breast cancer, addressing blind spots in current treatment strategies due to ill-defined diagnostic criteria. Leveraging scRNA-seq technology through SL, transcriptomic signature-driven drug repurposing and computational validation allows for more personalized treatment options while reducing laboratory costs in development of new treatment strategies.

Research theme 1: Bioinformatics and Data Science
Research theme 2:
Research theme 3:

Presenter's Name: Bari, Amaan

Additional Author(s): Chang N, Madahey H, Hardy DB, Dhanvantari S

Abstract Title: Phytocannabinoid-induced Reprogramming of Mouse αTC1-6 cells

Abstract:
Introduction: In North America, the prevalence of maternal cannabis use and its potential consequences are concerning. Previous studies have demonstrated that gestational cannabis exposure increases the risk of pancreatic dysfunction for the exposed offspring later in life. The current belief is that the main phytocannabinoids (PCs) found in marijuana, cannabidiol (CBD) and fj9-tetrahydrocannabinol (fj9-THC), exert their effects on pancreatic islets through the endocannabinoid system (ECS). While this signaling pathway is well characterized as a regulator of insulin secretion in β-cells, its regulatory role in α-cells is less understood. Preliminary data from our lab suggests that both the ECS itself and the spatial distribution of glucagon are modified in α-cells exposed to CBD and fj9-THC, contributing to the overall outcome of cannabinoid-induced α-cell dysfunction. Based on these observations, we hypothesize that PC exposure results in alterations to ECS signaling and glucagon trafficking within pancreatic α-cells.

Methods: Mouse αTC1-6 cells were treated with 30 μM of either CBD or fj9-THC to simulate PC exposure and to assess potential cannabinoid-induced alterations. Gene expression of key components of the α-cell ECS was determined using qRT-PCR, and intracellular localization of glucagon was assessed using immunocytochemistry and confocal fluorescence microscopy, where the colocalization of glucagon with different cellular compartment identifiers was analyzed.

Results: Both CBD and fj9-THC treatments are expected to lead to an upregulation of ECS target genes, highlighting this pathway as an important regulator of cannabinoid-induced cellular alterations. Spatial distribution of glucagon is expected to be altered, with glucagon being observed away from the cell periphery and instead being colocalized with lysosomal markers, suggesting that glucagon secretion is disrupted by ECS signaling.

Discussion: Through these experiments, we aim to identify how CBD and fj9-THC induce changes in pancreatic alpha cells by exploring how critical components of the ECS and glucagon trafficking may be altered upon exposure to these PCs. These findings will lead to a better mechanistic understanding of cannabinoid-induced α-cell dysfunction, and they will contribute to ongoing efforts to elucidate the connections between cannabis consumption and long-term metabolic dysfunction.

Research theme 1: Cardiovascular, Respiratory Health, and Metabolic Diseases
Research theme 2:
Research theme 3:

Presenter's Name: Barboza, Rachel

Additional Author(s): Lin A, Liu E, Le Q, Ling C, Castellani C, Zhang Q

Abstract Title: The Molecular Characteristics of Granular Mitosis in Glioblastomas

Abstract:
Introduction: Glioblastoma is the most common malignant neoplasm of the central nervous system and has a poor prognosis with an average survival of 6 months. A high proliferative index, such as an increased mitotic rate, is a key feature of these high-grade tumors. "Granular mitosis" (GM) is a unique type of atypical mitotic figure observed exclusively in glioblastoma, but not other tumors. The molecular etiology of GM formation in glioblastoma is largely unknown.

Methods: To understand GM's pathogenesis, we used The Cancer Genome Atlas (TCGA) Glioblastoma Multiforme dataset (N=619). First, we identified patients who exhibited granular mitosis through the annotation of diagnostic tumor histology whole slide images. Using the patient's corresponding transcriptomic, epigenomic, and genomic data, we conducted differential gene expression, methylation, mitochondrial (mt) DNA, and copy number variation (CNV) analyses via linear mixed model regression after data cleaning and preprocessing. Where relevant, potential confounding factors such as sex and ethnicity were accounted for. Downstream in silico overrepresentation analysis will be performed to identify pathways and features of interest. Multi-Omics Factor Analysis (MOFA) will also be conducted to detect patterns by integrating these datasets to gain an in-depth understanding of the factors associated with GM. Genes that show differential methylation, gene expression, CNV, and mtDNA will be prioritized for further follow-up. Finally, clinical information will be correlated for associations with identified outcomes.

Results: There were 82 glioblastoma slides reviewed, and 53 glioblastoma cases were included for analysis (35 GM positive, 18 GM negative). The transcriptomic analysis results show that 60 genes are differentially expressed between glioblastoma patients who exhibit granular mitosis and patients who do not (FDR < 0.05; fold change >2). Functional enrichment through Gene Ontology (GO) analysis has identified associations with nucleosome assembly and organization (p = 3.19e-10), as well as chromatin structure (p = 1.18e-11).

Discussion: These preliminary findings demonstrate a molecular difference between patients who exhibit GM and those who do not. As additional diagnostic slides are annotated, more patient data will be included in our findings. Additionally, they provide a basis for further analysis of differential expression for patients with high and low concentrations of granular mitosis.

Research theme 1: Bioinformatics and Data Science
Research theme 2: Cancer Biology
Research theme 3: Pathobiology of Neurologic Diseases

Presenter's Name: Lim, Samantha

Additional Author(s): Cecchini, MJ

Abstract Title: Comparative Analysis of ChatGPT 4.0 and Pathologists' Assistants in Generating Gross Descriptions of Surgical Specimens

Abstract:
Introduction: Artificial intelligence (AI) has shown remarkable advancements in various fields, including healthcare. In the domain of anatomic pathology, AI has been increasingly explored for its potential to improve diagnostic accuracy, efficiency, and workflow automation. One critical aspect of anatomic pathology is the generation of gross descriptions for surgical specimens, which provide crucial information regarding the macroscopic characteristics of tissue samples, aiding in subsequent histopathological analysis and diagnosis. This time-consuming task is traditionally performed by trained pathologists' assistants (PAs). This study investigates whether AI systems can effectively replicate the capabilities of PAs in generating accurate, comprehensive and informative gross descriptions from visual inputs, such as photographs of surgical specimens. It is hypothesized that ChatGPT 4.0 is capable of generating accurate and comprehensive gross descriptions given the proper visual inputs.

Methods: To test this hypothesis, 2 specimens of varying complexities were selected. Publicly available photographs of each specimen, featuring a scale, overall view and cross sections were sourced. A second year PA student analyzed each specimen photograph and wrote gross descriptions following LHSC standardized templates. Subsequently, a custom GPT was built using ChatGPT 4.0 by incorporating LHSC templates, guidelines for gross descriptions and sample gross descriptions. The specimen photographs were then inputted into the custom GPT for generation of a description. Both PA student and AI-generated gross descriptions were submitted to a pathologist for blind assessment, evaluating accuracy, comprehensibility and effectiveness.

Results: Preliminary results indicate that custom GPT gross descriptions are accurate, comprehensive and effective when provided with sufficient visual input. Furthermore, the pathologist was unable to identify which descriptions were AI-generated and which ones were written by the PA student.

Discussion: These findings demonstrate that given the proper guidelines and visual input, AI is capable of analyzing specimen photographs and writing accurate gross descriptions sufficient in aiding a pathologist in the diagnosis of a specimen. This may hold significant implications for the future of anatomic pathology, potentially leading to improvements in the accuracy and efficiency of pathological assessment in clinical settings.

Research theme 1: Digital Pathology
Research theme 2:
Research theme 3:

Presenter's Name: Lauzon-Young, Carolyn

Additional Author(s): Silva A, Sadikovic B, Relator R, Levy M, Bhai P, Kerkhof J, Rzasa J

Abstract Title: Defining Epigenomic DNA Methylation Biomarkers in Myeloid Malignancies

Abstract:
Introduction: Hematological malignancies encompass a wide range of cancer types, including myeloid malignancies which arise from hematopoietic stem or progenitor cells. Early detection of the location and type of cancer is essential to improving patient outcomes. Our lab has developed technology called EpiSign that uses genome-wide DNA methylation analysis to enable diagnosis of genetic disorders based on the presence or absence of episignatures. Episignatures are derived from recurring DNA methylation patterns, or biomarkers, associated with a common genetic or environmental etiology in a disorder specific population. The EpiSign test is currently able to detect episignatures of over 120 genetic and teratogenic disorders. We hypothesize existence of episignature profiles in hematologic malignancies which often involve driver mutations in epigenetic regulatory machinery. Our primary objective is to determine if DNA methylation profiling can be used to classify myeloid malignancies based on clinical diagnosis and genetic mutational subtypes.

Methods: DNA was obtained from the peripheral blood samples of patients with clinically diagnosed hematological malignancies including CML, MPN, and MDS, along with matched controls from the EKD. DNA methylation levels are evaluated using the Illumina Infinium EPIC bead chip arrays. The clustering of cases and controls is examined with Euclidian clustering and multidimensional scaling (MDS). A support vector machine (SVM) is used to evaluate the sensitivity and specificity of the biomarker for each cohort.

Results: Preliminary data shows evidence of episignatures in clinically defined myeloid malignancies subtypes. Data analysis revealed distinct and reproducible episignature patterns enabling separation between cases and controls in all cohorts. More clinically divers subtypes such as MPN showed a broader distribution of methylation profile between cases, while less clinically diverse subtypes such as CML showed a very uniform profile.

Discussion: Genome-wide epigenetic testing may be able to be used for the discovery of epigenetic biomarkers for hematological cancer diagnosis and pathological classification. Preliminary evidence suggests that distinct DNA methylation episignatures can be used to define and stratify different myeloid malignancy subtypes, and may be able to define genetic subtypes, enabling more accurate diagnostic classification of myeloid malignancies and reclassification of ambiguous genetic findings

Research theme 1: Bioinformatics and Data Science
Research theme 2: Cancer Biology
Research theme 3: Epigenetics

Presenter's Name: Taray-Matheson, Danielle

Additional Author(s): McLoughlin A, Min W

Abstract Title: The role of circHUWE1 in prostate cancer

Abstract:
Introduction: Prostate cancer (PCa) is the most common type of cancer and third leading cause of cancer mortality in Canadian men. PCa is typically manageable if detected early; however, some patients develop a more aggressive phenotype that is resistant to current therapeutics, highlighting a need for continued research to develop more efficacious treatment options. We have previously shown that circular RNA HUWE1 (circHUWE1) is upregulated in highly metastatic PCa cells; however, the specific role circHUWE1 plays in PCa is unknown. We aim to assess the role of circHUWE1 in PCa cell proliferation, migration, and invasion, and elucidate the molecular mechanism by which circHUWE1 may modulate PCa pathogenesis.

Methods: PC3 cells were transfected with circHUWE1 siRNA to perform loss-of-function experiments. Cell proliferation, migration, and invasion were assessed using CCK-8, scratch, and transwell assays, respectively. Expression of epithelial-to-mesenchymal transition (EMT)-related molecules was assessed using qPCR and western blot. Cell death and cell cycle were assessed using flow cytometry. Online binding prediction softwares were used to determine RNA binding proteins and microRNAs that may potentially interact with circHUWE1. An RNA pull-down assay was conducted to pull-down circHUWE1 complexes. qPCR and western blot will be performed to determine the potential binding partners of circHUWE1. Co-transfections will be conducted to confirm the relationship between circHUWE1 and its target molecules.

Results: Knockdown of circHUWE1 significantly reduced PC3 cell proliferation and migration but did not affect cell invasion. A reduction in mesenchymal marker protein expression was observed in cells transfected with circHUWE1 siRNA compared to controls. Transfection with circHUWE1 siRNA did not affect cell death or cell cycle phase relative to control cells. No changes in HUWE1 expression were seen in cells transfected with circHUWE1 siRNA, indicating circHUWE1 likely exerts its effects through a mechanism other than altering linear gene expression.

Discussion: Understanding the contribution and mechanism of circHUWE1 in PCa progression can contribute to the development of targeted therapeutics to prevent tumour metastasis and improve outcomes for patients with metastatic disease.

Research theme 1: Cancer Biology
Research theme 2:
Research theme 3:

Presenter's Name: Gholami, Hasti

Additional Author(s): Al KF, Figueredo R, Burton JP, Maleki SV

Abstract Title: The impact of gut microbiota on the response to immune checkpoint blockade in neuroblastoma tumours induced to be immunologically active

Abstract:
Introduction: Recent preclinical and clinical evidence suggests the gut microbiota can modulate anti-tumour immunity and affect the efficacy of immune checkpoint inhibitors (ICIs). However, the specific impact of the microbiota is contingent upon its composition, cancer type, and individual variables. This study elucidates the interplay between the gut microbiota and the immune phenotype of immunologically hot neuroblastoma tumours after induced mismatch repair deficiency (idMMR). Our laboratory has previously demonstrated that idMMR neuroblastoma tumours are more immunogenic than parental control tumour cells, have higher infiltration of T-cells, and have reduced tumour growth in immunocompetent mice. However, it is currently unknown whether changes in the immune phenotype of these tumours are linked to microbial composition. This study aims to provide mechanistic insights into the role of the gut microbiota on the immunogenicity of idMMR neuroblastoma tumours.

Methods: To investigate the role of the gut microbiota in idMMR neuro-2a (N2a) tumour progression and immune phenotype of tumours, immunocompetent 6-8-week-old female A/J mice were either administered phosphate-buffered saline (PBS) or an antibiotic cocktail (ABX) comprising ampicillin, metronidazole, vancomycin, and neomycin for ten days. Subsequently, mice were subcutaneously inoculated with N2a cells. Tumour volumes were monitored at 2–3 day intervals. Flow cytometry was used to assess the immunophenotypes of tumour-infiltrating lymphocytes (TILs), while 16S rRNA gene sequencing was used to analyze gut microbial composition.

Results: ABX treatment led to a less diverse gut microbiota composition, correlating with higher tumour volumes at 15-, 18-, and 20-days post-tumour cell inoculation compared to PBS-treated mice ($p<0.05$). A depleted gut microbiota promoted idMMR N2a tumour growth, evidenced by larger tumour volumes. Additionally, ABX-treated mice exhibited reduced levels of CD3+ -TILs, including CD4+- and CD8+-TILs. ABX-treated tumours displayed elevated levels of dysfunctional and exhausted CD8+ TILs.

Conclusions: This study demonstrates that in idMMR N2a tumours, a depleted gut microbiota promotes tumour growth and diminishes functional tumour-specific T-cell populations, rendering them more exhausted and dysfunctional. These findings advance our comprehension of the gut microbiota's role in shaping the tumour immune microenvironment, potentially impacting ICI sensitivity.

Research theme 1: Cancer Biology
Research theme 2: Infection, Immunity, and Inflammation
Research theme 3: Regenerative and Transplantation Medicine

Presenter's Name: Hird, Cody

Additional Author(s): Lawley B, Quiñones-Mateu ME

Abstract Title: Developing Chimeric Coronavirus Spike Proteins as Universal Vaccine Candidates

Abstract:
Introduction: The COVID-19 pandemic emphasised the need to shift to an anticipatory, rather than a reactive, form of pandemic control. Due to the rapidly evolving nature of SARS-CoV-2 and the coronavirus (CoV) genus, it is likely that future CoVs may instigate additional outbreaks. In this study, we constructed and characterized a series of chimeric CoV spike proteins to (i) pre-empt the evolution of human CoVs (hCoV) and (ii) evaluate these chimeras as potential universal CoV vaccine candidates.

Methods: Focusing on the spike, the most diverse CoV gene and responsible for viral tropism, we used Gibson Assembly to construct a panel of 24 chimeric hCoV spike genes. We exchanged the N-terminal domain (NTD) and receptor-binding domain (RBD) from seven hCoVs (HCoV-229E, HCoV-NL63, HCoV-OC43, HCoV-HKU1, SARS-CoV, MERS-CoV, and SARS-CoV-2 BA.1) into different CoV spike backbones. All parental and chimeric hCoV spike genes were confirmed by deep sequencing and their expression verified by qRT-PCR and western blotting. We generated CoV spike pseudotyped lentiviruses to characterise the receptor usage (tropism) and neutralisation profile of the parental and chimeric constructions.

Results: Most chimeric hCoV spike proteins were fully functional, with virus tropism (i.e., their ability to use ACE2, AP-N, and/or DPP4 receptors) mainly driven by the respective RBD and, in a few surprising cases, the NTD. Interestingly, parental and chimeric hCoV pseudotyped viruses were differentially neutralized by COVID-19 convalescent or vaccinated sera.

Discussion: In addition to the pandemics caused by SARS-CoV, MERS-CoV, and SARS-CoV-2, the four endemic hCoVs are responsible for up to 20% of all respiratory infections. The characterisation of our panel of functional chimeric hCoV spike proteins showcases (i) the plasticity and diversity of hCoV spike proteins and (ii) the potential for the generation of novel viruses by intra-genus recombination. More importantly, our ongoing studies will help us characterise their immunogenic properties, with the goal of testing them as potential universal CoV vaccine candidates.

Research theme 1: Infection, Immunity, and Inflammation
Research theme 2:
Research theme 3:

Presenter's Name: Sun, Gracie

Additional Author(s): McLean S

Abstract Title: The LinkUp Study – Evaluating the Outcomes of the 519Pursuit's LinkUp Mentorship Program & the Role of Mentorship in Social Inclusion for People Experiencing Homelessness in London, Ontario

Abstract: In Canada, 35,000 Canadians experience homelessness on any given night, with at least 235,000 people experiencing homelessness in a year. This is a concern as people experiencing homelessness experience worsened health outcomes alongside greater barriers to accessing healthcare. This is exacerbated by social exclusion which drives individuals to physically exclude themselves further through encampments; thus, subjecting individuals to greater health risks and increasing inaccessibility to support. 519Pursuit is a non-profit organization in London, Ontario which seeks to improve the social inclusion of the homeless community in London through the launch of the LinkUp program, a mentorship program to pair participants experiencing homelessness to a mentor. The purpose of the study is to understand the outcomes of the LinkUp program, the association of mentorship and social inclusion, and understand best practices for 519Pursuit to expand the program. Through a community-based participatory research approach in collaboration with the 519Pursuit, a qualitative narrative-phenomenological semi-structured interview study will be conducted with up to 15 mentor pairs. Interviews will be transcribed and undergo Braun & Clarke 2018 thematic analysis. The anticipated results of the study are to uncover the individual and group benefits of the program through building friendship and also broader implications on improving individuals' quality of life and aim to be revealed by April. In addition, the participants' experiences are valuable in understanding best-practices for the LinkUp program. These findings alongside discussing homelessness and mapping relevant stakeholders through a One Health approach will be used to broaden our understanding of the association between homelessness, mentorship, and social inclusion, and provide valuable opportunities for knowledge translation.

Research theme 1: One Health
Research theme 2:
Research theme 3:

Presenter's Name: Resendes Torrado, Maya

Additional Author(s): Khan ZA

Abstract Title: Assessing Hyperglycemic Memory Duration via ECM Gene Expression

Abstract:
Introduction: Diabetes mellitus is a prevalent chronic metabolic disease characterized by hyperglycemia and classified into type 1 (T1DM) and type 2 diabetes (T2DM). Conventional treatments focus on controlling blood glucose levels. Cohort studies have demonstrated the value of long-term intensive treatment in offsetting the onset of diabetic complications. As well as proposing the phenomenon known as hyperglycemic memory (HGM). HGM is when high glucose-induced cellular dysfunction continues after glucose normalization. Yet, the sustained duration of hyperglycemic memory remains unclear. Previous research has proposed that even short-term exposure followed by glucose normalization can elicit memory formation. However, the genome is highly dynamic, and these modifications may not persist following the normalization of glucose. Therefore, the research aim is to assess hyperglycemic memory duration using extracellular matrix (ECM) gene expressions as markers.

Method: In experiment 1, high-glucose (at 30mM) exposure for 7 days, following glucose normalization (at 5.5mM) for 7 days on human microvascular endothelial cells (HMEC) will be assessed. The affected cells will be prepared for RNA isolation on days 2, 7, 9, 11, and 14 post-seeding. Isolated RNA will be measured, and cDNA will be synthesized. Real-time qRT-PCR will be conducted on 4 ECM (Fibronectin (FN) and 3 collagen variants) primers and 2 housekeeping primers, followed by statistical analysis. In experiment 2, HMEC harvested from patients with T1DM and T2DM will be assessed and compared to statistical analyses from experiment 1. Direct RNA isolation will be conducted and measured, and cDNA will be synthesized. Real-time qRT-PCR will be performed using the primers referenced in experiment 1, followed by statistical analysis.

Results: An expected outcome may be elevated expression of ECM during high-glucose exposure, peaking at 7 days and returning to normal levels during glucose normalization. The expression levels of the collagens and FN may also vary, suggesting the complexity of ECM gene regulation and the potential for reversibility of memory formation with proper glucose control.

Conclusion: This study will demonstrate the duration of hyperglycemic memory and the potential of reversibility of altered gene expression, contributing to our understanding of memory formation and its impacts on diabetic complication development.

Research theme 1: Cardiovascular, Respiratory Health, and Metabolic Diseases
Research theme 2:
Research theme 3:

Presenter's Name: Wasif, Sumaiyah

Additional Author(s): MacDonald J, Perampalam P, Dick FA

Abstract Title: Investigating the Role of Netrin Signalling in High-Grade Serous Ovarian Cancer

Abstract:
Introduction: Ovarian cancer (OC) is the most lethal gynecological cancer, with high-grade serous ovarian cancer (HGSOC) being its most common subtype. OC spreads through the development of spheroids within the peritoneal cavity, allowing them to persist in the abdomen and rendering them resistant to surgery and mainstream therapeutics. A genome-wide CRISPR screen conducted in our lab identified Netrins and the MAPK pathway as essential for spheroid survival. Therefore, I hypothesize that Netrins enhance the survival of HGSOC cells and contribute to chemotherapy resistance.

Methods: To investigate MEK inhibition in various HGSOC cell lines under suspension and adherent conditions, crystal violet (CV) and trypan blue assays were used to determine viability and proliferation. To elucidate whether the survival signal is solely netrin-dependent, we will conduct epistasis tests by examining downstream interactions with netrin-receptor knockouts and MEK inhibitors in cells. Future work will involve assessing the therapeutic window of MEK inhibition and its correlation with netrin expression and immune regulation in both immunocompromised and immunocompetent mice. Additionally, we plan to investigate associations between netrin expression and surgical outcomes, therapy resistance, and other comorbidities in clinical samples.

Results: Based on CV and trypan blue assays, we determined that a dose of under 10nM was sufficient to inhibit 50% survival in HGSOC spheroids. Our findings also indicate that adherent, proliferating HGSOC cells exhibit a cytostatic response, whereas dormant spheroids display a cytotoxic response to MEK inhibition.

Significance: Investigating the role of netrin signaling in ovarian cancer is essential for providing molecular insights into mechanisms underlying therapy resistance, cancer dormancy, and disease progression, potentially leading to the development of cancer therapeutics to improve patient outcomes.

Research theme 1: Cancer Biology
Research theme 2:
Research theme 3:

Presenter's Name: Sharma, Shreya

Additional Author(s): McKinley G

Abstract Title: Investigation of the Environmental Impacts of the Cryptocurrency Industry

Abstract:
Introduction: Cryptocurrencies are digital currencies, used as alternative forms of payment or investment, and secured by cryptography. Concerns about resource usage and environmental impact have emerged as the industry grows and becomes more computationally intensive. Despite these concerns, there is still a gap in understanding the full extent of the industry's environmental impact. Therefore, this scoping review aims to describe the environmental impact associated with the cryptocurrency industry. To achieve this goal, the specific objective of this research is to review and synthesize existing scientific and non-scientific literature to better understand the environmental effects of cryptocurrency activities.

Methods: The scoping review methodology was adapted from the PRISMA Extension for Scoping Reviews (PRISMA-ScR) framework. Open-access scholarly and non-scholarly sources published in English between 2020 and 2023 from North America, China, and India were collected from Scopus, ProQuest, PubMed, and the Bielefeld Academic Search Engine.
Results: Of the 299 sources retrieved, 26 sources were selected for inclusion in this review based on eligibility criteria and access to full-text versions. Five of the 26 studies discussed cryptocurrency data centers' environmental consequences. Ten studies considered the environmental impact of cryptocurrency mining hardware. Sixteen sources discussed the electricity and energy needs of the cryptocurrency industry, emphasizing its role in greenhouse gas and carbon emissions. Eleven sources discussed mitigating the environmental impact of the cryptocurrency industry through regulatory recommendations, modifications to the cryptocurrency blockchain or energy sources, and changes in investment trends.

Discussion: The findings show the considerable environmental impacts of the cryptocurrency industry. The research highlights the multifaceted nature of environmental degradation caused by cryptocurrency activities and identifies opportunities for future research and action to promote sustainability within the industry.

One Health Relevance: This research is significant to the One Health approach as it underscores the interconnectedness between technological innovation, environmental sustainability, and social well-being. It highlights the need for collaborative efforts across animal, human, and environmental health sectors to holistically address the environmental impacts of emerging industries like cryptocurrency.

Research theme 1: One Health
Research theme 2:
Research theme 3:

Presenter's Name: Shin, Elly

Additional Author(s): Castellani CA, Arking DE

Abstract Title: Elucidating the Mechanism(s) of Mito-Nuclear Crosstalk

Abstract:
Introduction: Mitochondria are membrane-bound organelles of eukaryotic cells that play a critical role in cell functioning and homeostasis, such as ATP generation for cellular energy. They contain mitochondrial DNA (mtDNA), which exists in varying copies per cell (mtDNA-CN) and can be modified by environmental factors. Studies show mtDNA-CN's association with complex disease risks, possibly via the mitochondria's bi-directional crosstalk with the nucleus (mito-nuclear crosstalk). mtDNA-CN changes lead to modification of the nuclear DNA (nDNA), evidenced by methylation changes at multiple CpG sites upon mtDNA depletion, and induce changes in nuclear gene expression and levels of several epigenome-modifying metabolites. We aim to investigate the role of metabolites in the relationship between mtDNA-CN and the nDNA epigenome, and ultimately in disease risk.

Methods: A global metabolomics assay using chemical isotope labelling LC-MS will be performed on a TFAM KO cell model of mtDNA depletion to identify metabolites which may mediate the effect of mtDNA-CN on the nDNA epigenome. The role of these metabolites will be confirmed through association analyses with in-house matched methylation and gene expression data. To further explore the directionality of these changes and associated mechanisms, we will directly modify mtDNA-CN-associated CpG sites (previously identified in the lab) via the CRISPR dCas9-SunTag system. Successfully edited cell lines' mtDNA-CN will be quantified using qPCR and sent for global metabolomics analysis, as above.

Results: The metabolomics analysis is expected to identify changes in epigenome-modifying metabolite levels upon mtDNA depletion, leading to differential nDNA methylation patterns. Metabolites that have yet to be found to be associated with nDNA methylation will also be explored. CRISPR-edited cell lines are expected to show differential mtDNA-CN and corresponding differential global metabolite levels, identifying metabolites mediating this relationship.

Discussion: Metabolites associated with both mtDNA-CN and nDNA CpG variation will be considered candidates for further mechanistic studies. Further, metabolomics analyses of the edited cell lines will verify the bi-directional involvement of the identified metabolites. These results are expected to confirm causality and directionality, ultimately uncovering mechanisms contributing to mito-nuclear crosstalk and how these dynamics relate to health and disease.

Research theme 1: Bioinformatics and Data Science
Research theme 2: Epigenetics
Research theme 3:

Presenter's Name: Kim, Grace Eunbin

Additional Author(s): Khan ZA

Abstract Title: In vitro modeling of the Hematopoietic Stem Cell Niche using CD133+ stem cell overlay culture system

Abstract:
Introduction: Since Schofield's postulation in 1978 that hematopoietic stem cells (HSCs) in the bone marrow reside in a niche; extensive work has aimed to identify it. In vivo studies have revealed twofold sites as potential HSC niches: perivascular and endosteal. Given the dynamic nature of the stem cell niche and the heterogeneity of HSCs, continuously observing and analyzing stem cell behavior requires the complex functions of living bone marrow. Hence, to date, there has not been a successful in vitro model established. The research aims to create an in vitro perivascular niche model using CD133+ HSCs overlaid on isolated human dermal microvascular endothelial cells (HDEMC). The objective is to successfully recreate the in vitro perivascular niche, to determine the presence of long-term HSC cells via stem cell markers.

Methods: For the creation of the in vitro perivascular niche system, the base layer of HDEMC was plated at a density of 20,000 cells/cm2 on 12 well plates with Endothelial Growth Media (EGM; R&D systems), 20% FBS treated. 3 replicates, 3 experimental control conditions (CD133+ stem cell, CD133+ overlaid on HDMEC 2D culture, HDEMEC 2D culture only), and 3 time points (Day 1, Day 7, Day 14) were selected to observe the growth of cells. Then, the total RNA from each condition was isolated and extracted using RNeasy Mini Plus. TaqMan probe-based qPCR reactions were performed for Sca-1, CD133, Sox-2, Nanog, and ActB respectively.

Anticipated Results: Culturing HSCs with endothelial cells is expected to promote HSC maintenance and proliferation. The dynamic nature of HSCs, entering and exiting circulation near vascularized cells highlights the existence of a distinct perivascular niche. Increased expression of stem cell gene markers is expected in CD133+ overlaid on HDEMCs compared to CD133+ cultured alone. Additionally, the research aims to find critical differentiation time points for CD133+ HSCs in the perivascular culture system.

Conclusion: Understanding these interactions and the creation of a successful in vitro culture system of HSCs will provide valuable insights for potential therapeutic interventions in regulating HSC fate and functionality. Future directions of the study can be extended to overlay in vitro culture systems of osteoblasts to create the endosteal niche, or with adipocyte layers to understand microenvironments connected to hematologic malignancies to understand its suppressive effect in the expansion of HSCs.

Research theme 1: Cardiovascular, Respiratory Health, and Metabolic Diseases
Research theme 2: Regenerative and Transplantation Medicine
Research theme 3:

Presenter's Name: Potter, Maya

Additional Author(s): Donavan J, Arts E, Quiñones-Mateu M

Abstract Title: Early detection of SARS-CoV-2 variants of concern using a wastewater surveillance model

Abstract:
Introduction: Severe acute respiratory syndrome 2 (SARS-CoV-2) is the instigator of the coronavirus disease 19 (COVID-19) global pandemic that led to a dramatic loss of human life worldwide. The emergence of variants of concern that pose an increased risk to global public health exemplifies the necessity for timely epidemiological surveillance. Wastewater surveillance of SARS-CoV-2 has been an immensely valuable tool domestically in London, Ontario throughout the pandemic and provides a means of tracking disease prevalence and dynamics on a broad geographic scale. We have previously shown that London wastewater can be used to monitor the emergence and proportions of circulating SARS-CoV-2 variants of concern over time. While it is known that wastewater surveillance is an effective tool for epidemiological surveillance, whether it provides an effective means of detecting new viral variants earlier than traditional clinical testing remains uncertain.

Methods: To answer this question, wastewater was collected from five treatment facilities across London, Ontario between June 2021, and January 2023. We focused on samples collected between August and December of 2021 to explore the potential for early detection of the Omicron BA.1 variant. RNA was purified from the wastewater, reversed transcribed into cDNA, and nested PCR based on the SARS-CoV-2 spike gene was performed. Deep sequencing using the Illumina miSeq platform was employed to identify the emergence of Omicron BA.1 in the London population.

Results: Our results show that by using nested PCR with high sensitivity, wastewater surveillance can detect new viral variants up to two months before traditional clinical testing. We detected Omicron BA.1 in London wastewater samples in September of 2021, yet clinical surveillance methods did not detect this variant until November of 2021.

Discussion: These results highlight the effectiveness of wastewater surveillance as a method for epidemiological surveillance. Early detection of variants of concern permits the development of strategies to contain epidemic outbreaks. These data can ultimately be used to guide and inform public health decision-making in the future.

Research theme 1: Infection, Immunity, and Inflammation
Research theme 2:
Research theme 3:

Presenter's Name: Mattekatt, Juhi

Additional Author(s): Elsayed S

Abstract Title: Investigation of Antimicrobial Stewardship in North American Indigenous Communities

Abstract:
Introduction: Antimicrobial resistance is a growing threat that requires stewardship strategies to limit the growth and spread of resistant pathogens. Indigenous communities in North America have historically been underserved, and this has likely resulted in a lack of adequate antimicrobial stewardship in these communities. In the present review, we aim to explore the quality of antimicrobial stewardship practices in North American Indigenous communities. This has been done by determining the appropriateness of antimicrobial prescribing practices in Indigenous communities; and by determining what antimicrobial stewardship strategies are currently present at health centres within Indigenous communities.

Methods: A narrative review was performed using literature found from Scopus, Embase, PubMed, Cochrane, CINAHL, and Web of Science. Search strings using key words were used to search these databases. Only English-language articles published between January 2000 and June 2023 were included. Critical appraisals of the included articles were conducted using CASP checklists.

Results: This review is currently in process and completed results will be presented on April 4th. This project is expected to find that there is excessive and inappropriate prescription of antibiotics by health centres targeted at Indigenous communities. A lack of appropriate stewardship strategies, and increased rates of antimicrobial resistant infections compared to non-Indigenous communities are also expected.

Discussion: This review expects to find gaps in the current approach to antimicrobial stewardship in North American Indigenous communities. Improper dispensation of antimicrobials due to a lack of stewardship practices contributes to the rise of resistant pathogens within these communities. Proper antimicrobial stewardship must be practiced by all communities that use antimicrobials. Thus, this project may emphasize the need for increased support to Indigenous communities so that antimicrobial stewardship practices can be integrated into routine clinical care for this patient population. Stewardship strategies can be implemented by increasing surveillance through a One Health approach, as well as by properly educating stakeholders, which can include both healthcare providers and patients.

Research theme 1: One Health
Research theme 2:
Research theme 3:

Presenter's Name: Brower, Brandon

Additional Author(s): Cecchini M

Abstract Title: Investigating the Recent Rise in Peritoneal Mesothelioma Cases in London and Area

Abstract:
Introduction: Malignant mesothelioma is a cancer that arises from the mesothelium, a membranous lining of the lungs (pleural mesothelioma) and the abdomen (peritoneal mesothelioma), among other organs. Mesothelioma is rare with a prevalence of approximately 1 per 100 000 and carries a poor prognosis, although these numbers vary across subtypes. Pleural mesothelioma is the most common subtype, accounting for approximately 80% of mesothelioma diagnoses, and is known to be caused by asbestos exposure following a lengthy incubation period. Relatively less is known about the peritoneal subtype, which accounts for about 10% of mesothelioma cases. It is unusual for London and area to see more than 1-2 peritoneal mesothelioma cases per year; however, this incidence has dramatically increased in recent years with 10 cases reported in 2023. The reasons underlying this case rise are unclear. Therefore, we conducted a chart review of all malignant mesothelioma cases in London and area from 2017 to 2023 to identify contributing factors to this concerning development.

Methods: To investigate the recent increase in peritoneal mesothelioma cases, we compiled a list of patients diagnosed with either pleural or peritoneal mesothelioma in a London and area hospital since 2017 (inclusive). We then collected relevant information including sex, age, location of residence, occupation, tobacco smoking, asbestos exposure, type of initial biopsy, mesothelioma subtype (i.e. epithelioid, sarcomatoid, biphasic or desmoplastic), initial treatment, and treatment outcome. All patient data was documented in excel. Graphs were created and data analysis was conducted using GraphPad Prism.

Results: Our initial analysis has revealed a clear rise in peritoneal, but not pleural, mesothelioma cases over the past 7 years. Our data have also revealed that peritoneal mesothelioma cases are significantly more likely to have never smoked and worked a non-industrial job compared with pleural mesothelioma. Finally, linear regression of first-line treatment for pleural mesothelioma shows a significant trend away from chemotherapy and towards immunotherapy since 2017.

Significance: This work has clear public health implications, considering that environmental influences could be driving this drastic rise in peritoneal mesothelioma cases. Identifying these factors early is of tantamount importance to inform recommendations or other changes to prevent further cases and potentially save

Research theme 1: Test Utilization, Optimization and Quality Assurance
Research theme 2:
Research theme 3:

Presenter's Name: Chang, Esther

Additional Author(s): Guo J, Tinney-Dickinson D, Carmichael J, Darling M, Hamilton D

Abstract Title: The Impact of Bone Morphogenic Protein on SATB2-Mediated Heterotopic Gingival Ossification

Abstract:
Introduction: Peripheral ossifying fibromas (POFs) are gingival lesions that present with nidi of bone and are proposed to originate from the periodontal ligament (PDL). Though typically painless and easily resected, severe cases cause visible intraoral abnormalities that are detracting to patient mental health. POFs also show consistent nuclear expression of SATB2, an osteoinducive transcription factor. In recent studies, SATB2 is shown to be upregulated by bone morphogenic protein 2 (BMP-2) in mesenchymal cells. This study attempts to determine the effect of BMP-2 on SATB2 expression and ossification rate in human gingival fibroblasts (hGFs) and human periodontal ligament (hPDL) fibroblasts. It also aims to clarify the origin of POFs by elucidating which periodontal cell types are capable of ossifying. We hypothesize that BMP-2 will upregulate SATB2 expression and ossification rate in hPDL fibroblasts, but not hGFs.

Methods: Healthy hPDL fibroblasts and human gingival fibroblasts (HGFs) were cultured, stained, and analyzed for SATB2 expression via immunofluorescence staining. Furthermore, healthy hGFs were cultured in osteogenic cell culture media and are being treated with BMP-2 concentrations of either 0 ng/mL, 125 ng/mL, 250 ng/mL, 500 ng/mL, or 1000 ng/mL every Tuesday and Friday over four weeks. Control cell cohorts received Dulbecco's Modified Eagle Medium (DMEM) without BMP. These cell cultures will be stained with Alizarin Red S to assess for mineralization after the four weeks are completed. This process will be repeated for hPDL cells.

Results: Both healthy hGFs and hPDL fibroblasts showed nuclear expression of SATB2. Furthermore, after the first week of BMP treatment, when analyzed using phase microscopy, BMP-2 concentration and hGF ossification appeared to share a positive association until concentration surpassed 125 ng/mL. At the higher concentrations, less mineralization was seen and hGFs underwent increased rates of apoptosis. The DMEM control group showed no mineralization. We expect to see these results reflected in the Alizarin Red S stains.

Discussion: The results weaken the theory that POFs originate from the PDL, as both healthy hGFs and hPDL fibroblasts express SATB2. They also suggest that the effect of BMP on hGF ossification is dose dependent. Effects of BMP on varied populations of periodontal fibroblasts will be explored by repeating the four-week treatment with hPDLs.

Research theme 1: Infection, Immunity, and Inflammation
Research theme 2: Oral Biology and Medicine
Research theme 3:

Presenter's Name: Liang, Derick

Additional Author(s): Shooshtari P

Abstract Title: Application of Machine Learning in Predicting Gene Expression Profiles of Individual Cells Using Their Chromatin Accessibility Activities

Abstract:
ntroduction: Multi-omic profiling integrates diverse 'omics' data to understand biological systems, crucial for elucidating disease mechanisms and advancing personalized medicine. However, experiments to find multi-omics data can be extremely expensive and when produced, variations in sample preparation, data acquisition, and processing can lead to inconsistent and non-comparable results across different studies or platforms. To address the challenges in extracting multiple modalities from a single cell, recent research has focused on computational methods that can infer these modalities. BABEL, developed by Wu et al., represents a computational solution, predicting single-cell RNA or ATAC sequences from one another. Despite its capability, BABEL's prediction accuracy diminishes when applied to untrained cell types or species. This research evaluates BABEL's performance on expanded datasets across various cell types and species, aiming to enhance its predictive accuracy for broader applications in biomedical research.

Methods: To accomplish this aim, we will utilize four models developed using BABEL's machine learning algorithm: the original Wu et al. model (control), a second model incorporating additional human cell types, a third substituting human cells with mouse cells to maintain dataset size but introduce species diversity, and a fourth model combining the approaches of models two and three, using more datasets and cell types from both species. The impact of expanding training datasets and integrating diverse species on BABEL's performance will be assessed through density plots and correlation coefficients between predicted and experimental results.

Discussion: Improving BABEL's predictive accuracy with diverse cell types and species could make advancements in multi-omic studies, enabling easier, efficient comparative analyses. This advancement accelerates research through computational efficiency, reducing traditional sequencing costs and time. It could also enhance disease research and large-scale screenings, providing insights into population genetics and treatment responses, marking a significant step forward in utilizing computational models for complex biological data analysis.

Research theme 1: Bioinformatics and Data Science
Research theme 2: Epigenetics
Research theme 3: Test Utilization, Optimization and Quality Assurance

Presenter's Name: Pan, Nachuan Harrison

Additional Author(s): Karimi AH, Zeng PYF, Barrett JW, Nichols AC

Abstract Title: The Therapeutic Potential of Naporafenib in Anaplastic Thyroid Carcinoma

Abstract:
Introduction: The incidence rate of thyroid cancer has significantly increased over the past few decades. The vast majority of these cases are papillary thyroid carcinoma typically with excellent prognoses; in contrast, anaplastic thyroid carcinoma (ATC) is a rare and highly aggressive subtype with an almost 100% mortality rate. Recent approval of RAF inhibitor (dabrafenib) and MEK inhibitor (trametinib) for a subset of ATC patients with BRAF V600E mutation has transformed the treatment landscape. Besides the standard treatment, naporafenib, a type II pan-RAFi, has emerged as an effective anti-tumour agent based on the data from our patient-derived xenograft model. Our research group is interested in characterizing the anti-tumour efficacy of naporafenib and elucidating its effect on tumour microenvironment using an immunocompetent mouse model.

Methods: To determine the drug sensitivity of ATC cells, we assessed naporafenib's cell line-specific IC50 by performing dose-response experiments on both human and murine ATC cell lines. Based on the results, we selected two naporafenib-sensitive human cell lines ASH3 (BRAF WT) and SW1736 (BRAF V600E) for a 24-hour naporafenib treatment followed by a reverse-phase protein array (RPPA) assay to examine changes in key protein pathways. We then injected murine ATC cell line TBP-3743 into immunocompetent mice to test the anti-tumour efficacy of naporafenib. Tumour volumes were measured daily as the primary parameter to evaluate its anti-tumour effects.

Results: The human ATC cell lines demonstrated varying levels of sensitivity to naporafenib while the murine cell lines were deemed sensitive to our drug of interest. The RPPA results suggested differential phosphorylation of CRAF, a member of the RAF family, in both cell lines following naporafenib treatment. The results of our syngeneic murine model showed naporafenib inhibited tumour growth compared to the control group.

Discussion: ATC is an uncommon yet fatal cancer that preferentially affects the elderly. Unfortunately, clinical and translational investigations have been dampened by its rarity. Our collective work suggests that naporafenib can control tumour growth by inhibiting BRAFV600E in the MAPK signaling pathway, promoting a compensatory increase in phosphorylation of CRAF. Finally, our in vivo results demonstrated that naporafenib can stabilize murine ATC progression, suggesting its potential to be incorporated into future combination therapies.

Research theme 1: Cancer Biology
Research theme 2:
Research theme 3:

Presenter's Name: Derakhshan Nazari, Mohammad Hossein

Additional Author(s): Asfaha S, Shooshtari P

Abstract Title: Data Integration to Uncover Cell Type-Specific Regulatory Mechanisms Driving Risk to Inflammatory Bowel Disease

Abstract:
Introduction: Understanding the pathogenesis of Inflammatory Bowel Disease (IBD) remains a challenge due to the disease complexity. Previous studies suggest that IBD is an autoimmune disease that arises in genetically susceptible individuals. Genome-wide association studies (GWAS) have identified > 200 genomic risk loci associated with IBD. Most IBD GWAS risk variants (i.e., SNPs) are in non-coding regions, particularly in open chromatin regions in immune cells. However, the role of IBD risk SNPs in dysregulating genes within specific cell types is unknown. We used a data integration approach to better understand the cell type-specific gene regulatory mechanisms underlying IBD.

Methods: We first conducted a fine-mapping analysis of an IBD GWAS dataset (~60,000 samples) to identify credible interval (CI) SNPs; i.e., the SNPs likely to be causal. We then integrated these SNPs with the sequence-based data of 485 transcription factors (TFs) to assess if different alleles of any of these SNPs may change their binding affinities, in support of their gene regulatory effects. We called these SNPs, effect-SNPs. Leveraging single-cell ATAC sequencing (scATAC-seq) data from ~10,000 peripheral blood mononuclear cells (PBMC), we identified cell type-specific chromatin accessibility peaks overlapping effect-SNPs. Lastly, we measured co-accessibility between the peaks harboring effect-SNPs and the open chromatin peaks overlapping genes promoters to predict candidate genes.

Results: Our analysis identified 1,767 CI SNPs out of ~31,000 IBD-associated SNPs. 867 of these SNPs revealed to significantly affect the binding affinity of 269 TFs. Through mapping effect-SNPs to peaks in 10k PBMC scATAC-seq data, we identified 117 SNPs affecting 112 TFs, and located on 85 open chromatin sites in 12 immune cell types. Notably, CD14 monocytes exhibited the highest number of candidate risk-mediating peaks (9 peaks, 17 TFs). After performing differential accessibility analysis to identify cell type-specific peaks and measuring their co-accessibility with gene promoters, 15 SNPs in 13 regulatory sites were found to control the expression of 113 genes through 112 promoters via 28 TFs in eight immune cell types, among which CD14 monocytes were found to have the highest number of genes.

Discussion: Our findings suggest that CD14 monocytes play an important role in driving IBD risk, as evidenced by their open chromatin sites harboring risk SNPs affecting TFs and dysregulating target genes.

Research theme 1: Bioinformatics and Data Science
Research theme 2:
Research theme 3:

Presenter's Name: Tran, Michael

Additional Author(s): Poon A

Abstract Title: Investigating the role of surface-exposed proteins in virus evolution

Abstract: This project aims to investigate the evolutionary dynamics of human viruses, with a focus on the role of surface-exposed proteins and their encoding genes in viral adaptability and immune system interactions. Viral diseases, such as the COVID-19 pandemic, highlight the importance of understanding viral evolution due to their significant impact on global health and economies. Surface-exposed proteins in particular are crucial for virus-host cell interactions and immune evasion. The study aims to determine if genes encoding surface-exposed proteins experience higher rates of adaptation compared to other viral regions due to the intense selection pressure from immune system interactions. A dataset of over 4000 Hepatitis C Virus (HCV) RNA sequences was collected from Genbank and analyzed to assess selection pressures, with a focus on synonymous versus non-synonymous mutation rates. After alignment with MAFFT, the sequences are organized into their genotypes and subtypes and further into protein-coding genes. FUBAR analysis with hyphy produces heatmap fingerprints to visualize the selection pressures across the HCV genome, highlighting areas and trends of evolutionary change and especially differences between genes and genotypes. The research also incorporates machine learning, using image recognition to classify and label gene fingerprints based on their encoding of surface-exposed proteins. This innovative approach aims to bypass the complexity of high-dimensional data analysis typically associated with such studies. The significance of this research lies in its potential to enhance our understanding of HCV's evolutionary mechanisms and immune evasion strategies. The findings can inform vaccine and antiviral drug development, providing insights into the adaptability of HCV and possibly other rapidly mutating viruses, and improving preparedness for future viral threats.

Research theme 1: Bioinformatics and Data Science
Research theme 2: Infection, Immunity, and Inflammation
Research theme 3:

Presenter's Name: Lockau, Laura

Additional Author(s): Tweedie EJ, Smith SJ

Abstract Title: A case of post-transplant progression in a cardiac allograft with pre-existing transthyretin amyloidosis

Abstract:
Introduction: Cardiac amyloidosis represents a form of restrictive cardiomyopathy caused by amyloid infiltration in cardiac muscle. This syndrome is classified based on the precursor protein comprising the amyloid deposits, with the most common types being transthyretin amyloidosis, which has both wild-type and hereditary forms, and light chain amyloidosis. We outline the case of a patient who underwent cardiac transplantation in which amyloid infiltration was unexpectedly found within the allograft on post-transplant biopsies.

Methods: This case report reviews histology from multiple antemortem cardiac biopsies along with findings from the postmortem examination conducted seven years post-transplant.

Results: Postmortem examination revealed a heavy (805 g, normal range for weight 244-425 g) heart with marked concentric hypertrophy (left ventricle thickness 2.4 cm, normal range 1.2-1.5 cm) and a firm, waxy, pale myocardium. Allograft atria were dilated and showed patchy, granular endocardial plaques. Histologically, widespread interstitial deposition of amyloid protein throughout the myocardium (around 50% of myocardial tissue) as well as atrial endocardial amyloid deposits were highlighted with Congo red and transthyretin immunohistochemical stains. Given prior adequate function of the allograft, we postulate that there was ongoing deposition of the patient's transthyretin protein, causing further progression after transplantation.

Discussion: The discovery of cardiac amyloidosis in an allograft post-transplant represents an unusual clinical circumstance with important implications for transplant recipient health. No further donor information is available in this case. Familial-type amyloid was expected, but no pathogenic mutations were identified on genetic analysis of the allograft. Over the seven years post-transplant it is unclear why amyloid continued to accumulate; precedent and significant research in this area are lacking. We explore the possibility of progressive post-transplant wild-type amyloid deposition complicating pre-existing transthyretin amyloidosis in the allograft of a recipient without evidence of systemic amyloidosis.

Research theme 1: Cardiovascular, Respiratory Health, and Metabolic Diseases
Research theme 2:
Research theme 3:

Presenter's Name: Reyes-Ballesteros, Bernardo

Additional Author(s): Lawley B, Allais MJM, Kuang J, Hernández LC, Hird C, Bird TW, Comoletti D, Quiñones-Mateu ME

Abstract Title: Would SARS-CoV-2 be able to infect mammals relevant to Aotearoa New Zealand?

Abstract:
Introduction: Across vertebrate species the ACE2 genes are relatively conserved. The spike protein is mostly responsible for coronavirus binding and cell membrane fusion process using the ACE2 for virus entry to the host cell. During the last three years multiple in silico, in vitro, in vivo and/or surveillance studies have identified a variety of domestic/ wildlife animals susceptible to SARS-CoV-2 infection.

Methods: We generated cell lines stably expressing ACE2 orthologs from some of the most relevant animals in New Zealand, i.e., cattle, sheep, ferret, stoat, rabbit, common brushtail possum, rat, European hedgehog; including human and bottlenose dolphin as controls, to then characterize their susceptibility to infection by 22 pseudotyped lentiviruses containing the spike glycoprotein from SARS-CoV-2 variants, as well as β-coronavirus and other β-coronaviruses.

Results: ACE2 from rats, rabbits, cattle, and European hedgehog have limited susceptibility to infection by SARS-CoV-2 spike pseudotyped viruses. ACE2 proteins from sheep, ferret, stoat, common brushtail possum, and bottlenose dolphin seem to support binding and entry of spike pseudotyped viruses.

Discussion: Further studies are needed, not only to verify the susceptibility of these animal species to SARS-CoV-2 and/or other coronaviruses, but to surveil for the potential risk for SARS-CoV-2 reverse zoonosis.

Research theme 1: Infection, Immunity, and Inflammation
Research theme 2:
Research theme 3:

Presenter's Name: Limo, Luis

Additional Author(s): Donovan J, Frisbee S, Gomaa N

Abstract Title: Unraveling the Influence of the Exposome on the Human Oral Microbiome: A Scoping Review in the One Health Approach

Abstract:
Introduction: The human oral microbiome (HOM), a dynamic ecosystem within the oral cavity, comprises diverse microbial communities influenced by various factors and lifelong exposures, collectively known as the exposome. Disruptions on it can result in dysbiosis, inflammation, and infections. Our study aligns with the One Health approach, aiming to map the literature on exposomes' diverse impacts on HOM, while critically evaluating the evidence quality.

Methods: Following the PRISMA-ScR reporting guidelines, we undertook a scoping review including open access peer-reviewed studies conducted in humans, and published in English. We searched Medline, Embase, PsycInfo, Scopus, Web of Science, CINAHL, and used JBI critical appraisal tools to assess the quality of the evidence.

Results: We included 29 studies in our review, 28 of which were observational with the longest follow-up period of 5.5 years. The oldest reference corresponds to a cross-sectional study conducted in Poland, in 2013, and the most recent being in 2023. Most of the studies focused on human-health associated factors, including chronic diseases, pregnancy, menopause, and aging demonstrated significant associations with quantitative and qualitative changes of pro-biotic bacteria associated with oral health. Factors related to animal interactions, such as pet ownership suggested the presence of common bacterial strains carrying antimicrobial resistance genes, suggesting a potential for cross-transmission between pet owners and their dogs. Environmental factors, including occupational exposures, were associated to disruptions in the microbial composition and diversity of oral microorganisms. Studies had moderate quality, using valid methods like in-vitro sequencing and bioinformatic analysis. However, some exhibited high selection bias and had a short follow-up time.

Discussion: The studies included in this review revealed that the HOM is a complex and dynamic ecosystem that interacts with various exposomes related to animal health and the environment. However, most of them focused on the impact of human health-related factors, such as disease conditions and their treatment, on the HOM. There was a lack of studies describing the impacts of communities besides bacteria on the oral microbiome, and limited detail on the mechanisms of interaction between exposures and their impact on the HOM, as well as longitudinal studies evaluating long-term effects on dysbiosis-related outcomes in the oral cavity.

Research theme 1: One Health
Research theme 2: Oral Biology and Medicine
Research theme 3:

Presenter's Name: Harris, Cole

Additional Author(s): Wang E, Chakrabarti S, Feng B

Abstract Title: The Role of miR-9 in Alzheimer's Disease

Abstract:
Introduction: Alzheimer's disease is a progressive neurodegenerative disorder that affects the brain and causes a gradual decline in cognitive and functional abilities. Epidemiological studies have shown that diabetic patients have an increased risk of developing Alzheimer's disease. Excessive and pathological vascular remodeling that is a hallmark of diabetes could underlie the increased risk of developing Alzheimer's. A microRNA, miR-9, shows altered expression in experimental models of diabetes, and might mediate glucose-induced endothelial changes. However, the effects of miR-9 on the hippocampus in diabetes are still not clear. We hypothesize that diabetes-mediated changes in vascular miR-9 generate Alzheimer's-associated alterations in the brain.

Methods: To test this hypothesis, we created an miR-9 transgenic mouse model with endothelial-specific overexpression of miR-9. C57BL/6 wild type and miR-9 transgenic mice were injected with streptozotocin to induce diabetes, and then hippocampus tissues were collected. We then analyzed the expression of genes related to Alzheimer's using SanPrep Column microRNA Miniprep kits and RT-qPCR, specifically caspase 3, bcl-xl, amyloid beta, and tau proteins. We will use ELISA to determine the related protein levels, and staining to observe histological changes associated with Alzheimer's disease.

Results: Our results show higher expression of caspase 3 and lower expression of bcl-xl in B6 wild type diabetic mice than in B6 wild type control mice. We expect to see similar expressions of caspase 3 and bcl-xl to the B6 control mice in both diabetic and control miR-9 transgenic mice. We also expect to see a similar pattern with amyloid beta and tau, similar expression in the B6 control, miR-9 control, and miR-9 diabetic mice, with higher expression in B6 diabetic mice. Finally, we expect to observe more frequent histological changes associated with Alzheimer's disease in the diabetic B6 mice compared to the other groups.

Discussion: These findings show that diabetes increases the expression of Alzheimer's associated changes in the hippocampus. We also expect these findings to demonstrate the protective role of miR-9 in diabetes-mediated alterations in the brain associated with Alzheimer's, providing a novel mechanism and possible future therapy for Alzheimer's disease.

Research theme 1: Cardiovascular, Respiratory Health, and Metabolic Diseases
Research theme 2: Pathobiology of Neurologic Diseases
Research theme 3:

Presenter's Name: Halka, Felobater

Additional Author(s): Jackson-Boeters L, Darling M

Abstract Title: S100A7 Levels as a Marker for Predicting Malignant Transformation in Actinic Cheilitis

Abstract:
Introduction: Actinic cheilitis (AC) is an oral potentially malignant disorder (OPMD) that has the potential to transform into lip squamous cell carcinoma (LSCC). S100A7, a calcium-binding protein that is predominantly expressed in skin, is typically found at high levels in hyperproliferative skin diseases, such as AC. We have previously shown S100A7 to be a potentially useful biomarker for identifying OPMDs at risk of malignant transformation. Based on this background information, we hypothesize that high levels of S100A7 in AC are a positive predictor of malignant transformation.

Methods: Formalin fixed paraffin embedded tissue samples were immunohistochemically stained for S100A7. QuPath image analysis software was used to quantitate the levels of S100A7 in samples of normal controls, high-risk controls, low-risk controls, AC, and LSCC. The 5-year risk of malignant transformation was analyzed using an S100A7 immunohistochemistry-based signature algorithm (S100A7 ARS). Appropriate statistical analysis will be used to determine any correlation between S100A7 levels and malignant transformation.

Results: It is expected that S100A7 levels will be significantly increased in AC compared to normal and low-risk controls. A positive correlation between S100A7 levels in AC and malignant transformation is expected. AC cases which have transformed are expected to have higher S100A7 levels and S100A7 ARS risk than control tissues.

Discussion: These results should provide an insight into the association between S100A7 levels in AC and the risk of malignant transformation. The S100A7 ARS has been shown to have a role for risk stratification in malignant transformation of OPMDs. This study, along with future studies, may lead to S100A7 being established as an important biomarker in OPMDs and identify lesions which require early treatment prior to malignant transformation. In conclusion, it is expected that the findings of this study would support the hypothesis that S100A7 levels serve as a positive predictor of malignant transformation of AC.

Research theme 1: Oral Biology and Medicine
Research theme 2:
Research theme 3:

Presenter's Name: McCullagh, William

Additional Author(s): Gunaratnam L

Abstract Title: Regulation of danger signalling in proximal tubule epithelial cells

Abstract:
Introduction: Acute Kidney Injury (AKI) describes sudden loss of kidney function and is most commonly caused by renal ischemia-reperfusion injury (IRI). IRI leads to cellular ATP depletion and the production of reactive oxygen species, which can result in regulated necrosis of tubular epithelial cells in the kidney. Proximal tubule epithelial cells (PTECs) are particularly prone to IRI due to high-energy requirements and poor glycolytic capacity.

Uncleared necrotic cells lose membrane integrity, resulting in the release of intracellular contents into the extracellular milieu, which then serve as "danger" signals which trigger "sterile" inflammation (necroinflammation). Danger signals such as High Mobility Group Box-1 (HMGB1) bind to innate immune receptors (e.g. Toll-like receptor) on parenchymal and innate immune cells within the kidney and promote secondary tissue damage.

Kidney injury molecule-1 (KIM-1) is a glycoprotein receptor specifically upregulated on the apical membrane of PTECS during AKI, transforming them into phagocytes for the clearance of necrotic cell debris.

The Gunaratnam Lab has previously shown that the clearance of necrotic cells by KIM-1-expressing PTECs is essential for limiting necroinflammation and enabling tissue repair following AKI. However, it is unclear how the expression of KIM-1 on PTECs affects the cellular response to danger molecules released from cells undergoing necrosis during AKI. Our project aims to determine if KIM-1 expression on PTECs affects the cellular response to danger molecules released from necrotic cells. We hypothesize that KIM-1 expression will dampen the pro-inflammatory response of PTECs exposed to necrotic debris/danger molecules.

Methods: To test this hypothesis, we will culture a stable line of human tubule epithelial cells. Next, we will knockdown the KIM-1 protein via viral transduction, verifying the knockdown via western blot. We will then expose the cells to necrotic cellular debris and NK-kB phosphorylation via western blotting. We will also use PCR to assess mRNA expression of IL-6, IL-1, TNF-a and other inflammatory signalling markers.

Results: We anticipate our KIM-1 knockdown cell line will exhibit higher downstream levels of inflammation following initial treatment with necrotic cell debris.

Research theme 1: Infection, Immunity, and Inflammation
Research theme 2: Regenerative and Transplantation Medicine
Research theme 3:

Presenter's Name: Greasley, Adam

Additional Author(s): Zheng X

Abstract Title: Circular RNA HIPK3 Regulates Mitochondrial Apoptosis through Binding to ACAD9 and Ndufv1

Abstract:
Introduction: Ischemia reperfusion injury (IRI) induced cardiomyocyte apoptosis remains a leading complication of heart transplantation and a significant risk for graft failure. Our previous work showed that circular RNA HIPK3 (circHIPK3) is crucial for cardiomyocyte survival following IRI induced apoptosis. Knockdown of circHIPK3 lead to an increase in mitochondrial pro-apoptotic signaling, and knockdown + IRI lead to increased cell injury and death in HL-1 cardiomyocytes. In the present study, we attempt to decipher the mechanism by which circHIPK3 levels control apoptosis in HL-1 cardiomyocytes. We hypothesize that circHIPK3 stabilizes mitochondrial proteins and absence leads to decrease mitochondrial stability and increased cell injury during IRI.

Methods: To test this hypothesis, we first conducted a pull-down assay of circHIPK3 in HL-1 cardiomyocytes coupled with mass spectrometry to identify bound proteins of interest. Following this, circRNA-protein interactions will be confirmed by circHIPK3-pull-down assays coupled with western blot and immunoprecipitation of target proteins coupled with qPCR to detect bound circHIPK3. To determine if circHIPK3 interacts with these proteins within the mitochondria, in situ hybridization of circHIPK3 will be coupled with immunocytochemistry and a mitochondrial stain and examined for co-localization. In addition, circHIPK3 copy number will be determined in total cytoplasmic extract and isolated mitochondria to quantify the distribution of circHIPK3 between the cytosol and the mitochondria.

Results: To date, our mass spectrometry results show that circHIPK3 pull-downs are enriched for acyl-CoA dehydrogenase family member 9 (ACAD9) and NADH:ubiquinone oxidoreductase core subunit V1 (Ndufv1), both are components of complex I in the mitochondria.

Discussion: ACAD9 and Ndufv1 are both nuclear encoded mitochondrial complex I proteins. During IRI, damaged mitochondrial proteins are often replaced and recycled to prevent mitochondria failure and cell death. Therefore, these early results indicate that circHIPK3 may play a chaperone or stabilizing role of these two proteins, to replace damaged components and prevent injury. However, the completion of this study and elucidation of the mechanism is required to confirm this mechanism of action.

Research theme 1: Cardiovascular, Respiratory Health, and Metabolic Diseases
Research theme 2:
Research theme 3:

Presenter's Name: Han, Seungwon

Additional Author(s): Olea-Popelka P, Leseni T

Abstract Title: Tuberculosis in an Urbanizing Kenya: Investigating the link between urbanization in the 21st century and human, bovine, and zoonotic tuberculosis

Abstract:
Introduction: Kenya is experiencing population growth and urbanization, where more people are moving to cities from rural communities. Urban areas are hotbeds for aerial tuberculosis (TB) amongst humans, and urban and peri-urban agriculture in poorly ventilated settings increase opportunities for bovine TB (BTB) and zoonotic TB (ZTB) transmission. A burgeoning urban population and increasing demands for milk and beef will exacerbate pre-existing challenges with human TB, BTB, and ZTB. Thus, the main goal of this research is to investigate how urbanization is linked to TB in Kenya in the 21st century. However, the current discourse about TB in Kenya is focused mainly on human TB.

Methods: To address the research gap, a scoping review was conducted to investigate the link between urbanization and human TB, BTB, and ZTB in 21st century Kenya. Scientific peer-reviewed articles were sourced from the databases MEDLINE (Ovid), PubMed, Scopus, and Web of Science. Literature was selected using the software Covidence following PRISMA-ScR (Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews) guidelines.

Results: Most articles reported findings on human TB and identified risk factors for human TB associated with urbanization such as overcrowding and poverty. Urban slums were identified as being vulnerable to multidrug-resistant human TB. Fewer sources were found for BTB and ZTB, but slaughterhouses were cited as a risk factor for both. Furthermore, rural agricultural communities with limited knowledge on BTB and zoonoses were identified as being at risk for BTB and ZTB.

Discussion: These findings demonstrate urban and rural challenges in the management of human TB, BTB, and ZTB in Kenya. Both urban and rural challenges are heightened by socioeconomic factors, comorbidities, and lack of resources for diagnoses and surveillance. This research showcases the current lack of discourse and need for more research on BTB and ZTB in Kenya in relation to urbanization. The challenges of TB, BTB, and ZTB in an urbanizing 21st century Kenya necessitates a One Health (OH) approach especially since urbanization will continue to impact the environmental circumstances of animal and human interactions. TB in an urbanizing Kenya is a great challenge, but a successful approach against human TB, BTB, and ZTB in Kenya in collaboration with multisectoral OH stakeholders will set an example for similar challenges in other urbanizing countries.

Research theme 1: One Health
Research theme 2:
Research theme 3:

Presenter's Name: Grindrod, Natalie

Additional Author(s): Cecchini M, Brackstone M

Abstract Title: The digital pathology of TILs as a biomarker in breast cancer

Abstract:
Introduction: Breast cancer (BC) is the 2nd leading cause of cancer deaths for women worldwide, and 1 in 8 Canadian women will be diagnosed with BC. Tumour infiltrating lymphocytes (TILs) in BC is a prognostic and predictive biomarker. Good prognostic outcomes have been seen with high TILs in chemotherapy, but has not been fully explored with radiotherapy. Utilizing digital pathology allows TILs quantification to be more efficient. Local SIGNAL study slides previously collected were used, where patients underwent neoadjuvant chemoradiation or chemotherapy. We aim to assess how certain disease parameters and chemoradiation may affect TILs, assess TILs clustering, and how these may impact outcomes. Our hypothesis is that spatial mapping of the lymphocyte distribution will provide robust and accurate predictions of response to neoadjuvant therapy and therefore guide treatment decisions in BC.

Methods: 240 slides were digitized using the Aperio ScanScope, then image analysis performed using QuPath. This included doing cell detections, then training an object classifier with cell types. A pixel classifier was used to separate intratumoural and stromal TILs. Delaunay Triangulation will be used to assess clustering between cell types.

Results: Current results are still underway. Initial results show that chemoradiation does not diminish TIL population significantly differently from chemotherapy. Significance found between increased stromal and intratumoural TILs and pathological complete response in the chemotherapy group, similar trends seen in chemoradiation but no significance. Chemoradiation saw a significant increase in stromal TILs post-treatment in patients that achieved pathological complete response.

Discussion: This is the first study to apply TIL assessment to a well curated study of concurrent neoadjuvant chemoradiation patients. Outcomes and correlations between TILs and treatment modality will further the possibility of using TILs for prognosis and guiding treatment decisions. The semi-automated approach utilized in this study can be relatively easily deployed and will serve as a basis to build completely automated workflows that can be rapidly deployed in clinical practice. Despite theories of radiotherapy in BC completely diminishing the body's immune efforts and immune cells found in tissues, this is not necessarily true, and it may even induce immune response. Radiotherapy may indeed play an important role in the immune response for BC.

Research theme 1: Cancer Biology
Research theme 2: Digital Pathology
Research theme 3: Infection, Immunity, and Inflammation

Presenter's Name: Hosseini Naghavi, Nader

Additional Author(s): Shooshtari P

Abstract Title: Integrative Data Analysis to Uncover Transcription Factors Involved in Gene Dysregulation of Nine Autoimmune and Inflammatory Diseases

Abstract:
Introduction: Autoimmune and inflammatory diseases are a group of > 80 complex diseases caused by loss of tolerance of the immune system for self-antigens. The biological mechanisms of autoimmune diseases are largely unknown, preventing the development of effective treatment options. Integrative analysis of genome-wide association studies (GWAS) and epigenetic data has shown that the risk variants of autoimmune diseases are enriched in epigenetic regions of immune cells, supporting their role in gene regulation. However, we still lack a systematic analysis of transcription factors (TF) involved in disease gene regulation.

Methods: The binding sites of disease-related TFs can be affected at multiple genomic sites in a cell-type specific manner. In this study, we developed a statistical approach to assess enrichment of TFs in being affected by disease risk variants at multiple sites. We used GWAS data of nine autoimmune diseases and identified 99% credible interval (CI) SNPs (i.e., a set of SNPs which are likely to be causal) for each trait. We then integrated CI SNPs and DNase-I footprinting data of 376 samples comprising 35 unique cell types, and employed a probabilistic model to identify the CI SNPs that are likely to change binding of certain TFs at specific cell types. Finally, for each TF (out of 1,372 TFs), we used Fisher's Exact test to assess whether CI SNPs show enrichments in terms of changing the binding probability of that TF at multiple sites (FDR < 10%).

Results: Our analysis identified some TFs previously known to be relevant to autoimmune diseases (e.g. Ahr:Arnt for rheumatoid arthritis and SPI-B for multiple sclerosis), and some other less studied new TFs. The enriched cell types also varied across the traits, such as CD8 and Mobilized CD4 T cells for rheumatoid arthritis, and CD56 and Mobilized CD4 T cells for multiple sclerosis. Our ChromHMM analysis proved that our predicted DNase-I footprinting sites are active enhancers or promoters in the relevant cell types. Finally, our GREAT pathway analysis showed that the majority of the significant biological pathways are immune-related, an example of which is B cell adhesion pathway in multiple sclerosis.

Discussion: In this project we used a statistical framework to identify the significant effects of autoimmune diseases' risk variants on binding patterns of TFs. Our novel data integration method is general, and can be applied to other types of common complex diseases.

Research theme 1: Bioinformatics and Data Science
Research theme 2: Epigenetics
Research theme 3: Infection, Immunity, and Inflammation

Presenter's Name: Larsen, Frederikke

Additional Author(s): Good HJ, Shin AE, Derouet MF, Zhang L, Castellani C, Asfaha S

Abstract Title: Activation of a viral mimicry response inhibits colitis-associated cancer

Abstract:
Introduction: Colorectal cancer is the second leading cause of cancer death in Canada. A major risk factor for the development of colorectal cancer is chronic inflammation leading to colitis-associated cancer (CAC). We previously described a CAC mouse model in which tumors arise from DCLK1+ cells following loss of the tumor suppressor adenomatous polyposis coli (APC) and induction of colitis. Interestingly, both colitis and CAC are associated with DNA methylation changes that lead to altered gene expression. Moreover, inhibition of DNA methylation has recently been shown to lead to a viral mimicry response. The effects of DNA methylation on colonic tumorigenesis, however, is not known. Thus, we aim to investigate whether inhibition of DNA methylation leads to a viral mimicry response that inhibits CAC.

Methods: We examined the effects of DNA hypomethylation on CAC using Dclk1-CreERT2/Apcf/f/Dnmt1f/f mice which allowed for knockout (KO) of the DNA methyltransferase DNMT1 in DCLK1+ cells. Dclk1/Apcf/f/Dnmt1f/f and Dclk1/Apcf/f mice received three doses of tamoxifen followed by 2.5% dextran sodium sulfate (DSS) for five days to induce colitis. Fourteen weeks later, we assessed tumor number. In a separate cohort of Dclk1/Apcf/f mice treated with DSS, we compared tumor number in mice treated with six doses of 5-AZA-2'-deoxycytidine (5-AZA) versus vehicle. The effects of 5-AZA and DSS on DNA methylation were assessed using the Infinium Mouse Methylation BeadChip Array on colonic epithelial cells. RNA expression of endogenous retroviruses and interferon response genes were measured as a readout of viral mimicry. Next, we investigated how DNA hypomethylation affects tumorigenesis by crossing Dclk1/Apcf/f/Dnmt1f/f mice to MAVS KO mice and examining tumor number. Lastly, we induced CAC in WT or MAVS KO mice by treating with 10 mg/kg azoxymethane and 1.5% DSS followed by 5-AZA or vehicle.

Results: DNMT1 KO or 5-AZA treatment significantly decreased tumor number. 5-AZA treatment or DNMT1 KO led to DNA hypomethylation and subsequent upregulation of endogenous retroviral expression. Both 5-AZA treatment and DNMT1 KO led to increased expression of type I interferon response genes. KO of the type I interferon response gene, MAVS, reversed the anti-tumor effect observed with DNMT1 KO or 5-AZA treatment.

Discussion: Our findings demonstrate that DNA hypomethylation by 5-AZA or DNMT1 KO reduces colitis-associated tumorigenesis through activation of a viral mimicry response.

Research theme 1: Cancer Biology
Research theme 2: Epigenetics
Research theme 3:

Presenter's Name: Hamel-Smith Grassby, R. Leigh

Additional Author(s): Cecchini MJ

Abstract Title: Juvenile mucoepidermoid carcinoma of the lung with p40 negativity

Abstract:
Introduction: While common in the salivary glands, mucoepidermoid carcinomas (MEC) are far rarer in the lung and are commonly diagnosed using a combination of histological analysis and immunohistochemistry (IHC). The immunohistochemical staining of some MECs can be at odds with histologic features, often necessitating molecular testing to confirm the diagnosis.

Case: The patient was 7 years old and initially presented with pneumonia and a cough, a subsequent chest CT showing a mass in the left lower lobe. Intraoperative consultation showed a tan-white mass protruding from the airway, focally adherent to the bronchial wall. Frozen sections showed a proximal bronchial margin negative for malignancy. At time of grossing, the specimen was bisected longitudinally along the bronchial margin so that photographs of the mass in relation to the bronchus and adjacent mucous plugging could be taken. Grossly, the mass did not appear to involve the lung parenchyma or surrounding vascular structures. Histologically, the cytomorphology pointed towards a diagnosis of mucoepidermoid carcinoma, however the tumour did not stain positively for p40, which most tumours of this type do. This necessitated molecular testing to confirm the presence of a MAML2 rearrangement, and thus a diagnosis of mucoepidermoid carcinoma.

Discussion: Immunohistochemistry is a powerful diagnostic tool that has become the standard for diagnosis for many tumours. However, in the case of mucoepidermoid carcinomas, there is the potential for p40, an expected positive stain to present negative while still being a MEC. In most of these cases, the MEC involved is a histologic variant, but this case shows that even MECs with typical cytomorphology can be p40 negative. Caution should be exercised to avoid over-reliance on IHC so that p40 negative MECs are not misdiagnosed. While MECs will be grossed similarly to most central lung masses regardless of their immunological and molecular qualities, the gross examination will still play an important role in the staging and diagnosis of these tumours.

Research theme 1: Cancer Biology
Research theme 2:
Research theme 3:

Presenter's Name: Wang, Judy

Additional Author(s): Sposato L, Wang N, Baranchuk A, Ayan D, Chan D

Abstract Title: Investigating electrocardiographic abnormalities as predictors for Post-Stroke Major Adverse Cardiovascular Events

Abstract:
Introduction: Ischemic stroke (IS) in humans is linked to an increased risk of major adverse cardiovascular events (MACE). Electrocardiograms (ECGs) and troponin (cTnT) tests are conducted as part of standard stroke workup to detect concurrent myocardial infarctions (MI), but subtler indications of cardiovascular damage on these tests are often overlooked. Thus, this study hypothesized that certain ECG abnormalities and increased cTnT levels are associated with a higher post-stroke MACE risk. Specifically, the objective was to investigate if ECG abnormalities can predict PS-MACE alone or in combination with high cTnT levels, at 90 days and 12 months after the ischemic stroke.

Methods: This retrospective study drew from a cohort of 2000 patients, including those over 18 years old treated for stroke at the London Health Sciences Centre from 2019-2020. ECGs were collected, de-identified, and stored in the London Ontario Stroke Registry, then analyzed by the Kingston Health Sciences Center based on waveform morphology and time-series metrics. Next, this data was matched to patient outcomes such as MACE during follow-up.

Results: This study is currently ongoing, and final results will be presented by April 4th. However, it is expected that indicators of cardiac injury like elevated cTnT levels, and ECG characteristics such as ST depressions, negative T waves, and prolonged QRS intervals will be linked to PS-MACE outcomes.

Discussion: Following IS as a multidisciplinary disease, this study aims to bridge the neuro-cardiology awareness gap in cerebrovascular events. Pre-existing studies separately focus on ECG indicators of first-stroke risk, or target MACE following cardiovascular procedures. Yet, they neglect investigating ECGs as predictive of MACE post-stroke. Recognition of high-risk populations can improve stroke monitoring in racial groups more susceptible to IS or socioeconomically less able to access treatment, relating to social determinants of health and identification of relevant stakeholders as a component of a One Health approach to the disease. Therefore, the goal is to help develop a quick and inexpensive point-of-care tool for identifying patients at high risk of severe cardiovascular outcomes after a stroke.

Research theme 1: Cardiovascular, Respiratory Health, and Metabolic Diseases
Research theme 2: One Health
Research theme 3: Pathobiology of Neurologic Diseases

Presenter's Name: Osei-Owusu, Cornelius

Additional Author(s): Abud A, Nawal J, Wong C, Armas Machado M, Ryeed R, Sekar V, Guga S, Frisbee S

Abstract Title: Microcirculation and Critical Limb Ischemia

Abstract:
Introduction: Critical limb ischemia (CLI) is the end-stage manifestation of Peripheral Artery Disease and is characterized by pain at rest and tissue ischemia, with subsequent risk for necrosis and limb loss, and studies have reported a 1-year mortality rate ranging from 15-40%. The standard of care for CLI is revascularization by surgical or endovascular techniques. However, the outcomes of revascularization are poor, with reported risk of 1-year major adverse limb events (amputation, reintervention) as high as 37%. Reasons for poor outcomes are not well understood. One hypothesis is that revascularization restores bulk blood flow but there is unknown impact on the restoration of microcirculatory function, which is needed to restore tissue perfusion and function. Therefore, the purpose of this scoping review is to investigate the relationship between microcirculatory function and clinical outcomes in CLI patients.

Method: A systematic search was conducted on MEDLINE, EMBASE, Scopus and CINAHL to identify articles related to "microcirculation" and "critical limb ischemia", using a specific search strategy for each database. Study screening, for both title/abstract and then full-text, was conducted through Covidence based on a pre-determined inclusion and exclusion criteria. Data extraction is also being completed in Covidence, where information about study participants, microcirculation assessment technique, study design and key details relevant to the review question are being recorded.

Results: The search yielded 3551 studies across the four databases and 299 studies remained after title/abstract screening. Full-text screening, data extraction and synthesis remain ongoing. Thus far, 22 studies have undergone data extraction. Among these studies, there is a mix of experimental studies and observational studies, both longitudinal and cross-sectional. The two microcirculation measurement techniques used in these studies were transcutaneous oxygen pressure (TCPO2) and skin perfusion pressure. Amputation-free survival, major adverse limb events and wound healing were clinical outcomes commonly assessed.

Discussion: This study highlights the value of assessing the microcirculation as a tool for prognosis in CLI patients. Measuring the microcirculation could indicate which patients will benefit from revascularization and other interventions, which could guide clinical decisions and improve the cost-effectiveness and morbidity of treating CLI.

Research theme 1: Cardiovascular, Respiratory Health, and Metabolic Diseases
Research theme 2:
Research theme 3:

Presenter's Name: Kim, Sewon

Additional Author(s): Jackson-Boeters L, McCord C

Abstract Title: The utility of p16 and p53 immunohistochemistry staining to determine the prevalence of HPV in Oropharyngeal squamous cell carcinomas submitted by Ontario dentists

Abstract:
Introduction: The human papillomavirus (HPV) is a group of viruses that infects the genital and oral areas of the human body. The high-risk strains of this virus can cause oropharyngeal squamous cell carcinomas (OPSCC) and the incidence of HPV-related OPSCC is on the rise. This increasing trend is worrisome and the problem is compounded by insufficient discussion with patients about HPV-related oral cancers and inadequate screening of the oropharynx for this virus by dentists. In HPV related carcinomas p16, a tumour suppressor protein, is overexpressed and is often used as a surrogate marker of HPV. HPV infection can also cause degradation of p53, another tumour suppressor protein, and is a newly emerging surrogate marker for HPV infection. The aim of this study is to assess the prevalence of HPV-related OPSCC in a sample of biopsies submitted by dentists and dental specialists using p16 and p53 immunohistochemistry (IHC) staining.

Methods: Cases of OPSCC were collected from oral pathology archives from 2002-2020. p16 and p53 IHC staining was performed on all 55 of the selected specimens of OPSCC. p16 IHC staining was performed using CINtec histology kit which included mouse anti-Human p16INK4a antibody Cases were stained for p53 using the Dako Omnis automated slide stainer. A 3 point grading system was used to assess p16 staining. Cases were categorized into 5 groups according to the pattern of p53 expression. Statistical analysis is ongoing.

Results: Our cohort was predominantly male and the median age was 63. 14.5% of the cases included in our study are p16-positive and have an HPV-related p53 IHC. Approximately 12.7% of the samples were p16-positive but showed an HPV-unrelated p53 IHC pattern. These samples were classified as HPV-. Interestingly, one out of 55 cases were p16-negative but had a p53 IHC pattern associated with HPV which is not observed frequently in literature.

Discussion: Our results provide insight into the prevalence of p16 positive OPSCC that are submitted by Ontario dentists and dental specialists. The prevalence of p16-positive HPV associated OPSCC in our study was lower than that reported in the literature. This study has the potential to be educational material for dental providers on the importance of screening for HPV. This study could also have implications on the current standard of HPV assessment in biopsies which is the sole use of p16 staining, by assessing the complementarity between p16 and p53 immunostaining.

Research theme 1: Cancer Biology
Research theme 2: Oral Biology and Medicine
Research theme 3:

Presenter's Name: Houpt, Jacob A.

Additional Author(s): Baranova K, Chan NG, Moussa M

Abstract Title: Clear Cell Renal Cell Carcinoma with Hemangioblastoma-like Change in a Pediatric Patient with Tuberous Sclerosis Complex: the Morphological Intersection of Neuro- and Uro-pathology

Abstract:
Introduction: Hemangioblastomas of the CNS are benign neoplasms commonly arising in the posterior fossa, either sporadically or in the context of von Hippel-Lindau syndrome (VHL). These richly-vascular lesions contain branching capillary networks and markedly-pleomorphic stromal cells with expansive vacuolated cytoplasm, and characteristically feature an inhibin A+/CD10- immunohistochemical (IHC) profile, helping to differentiate it from metastatic clear cell renal cell carcinoma which is also rich in vasculature, can contain lipidized vacuolated cells, and may be seen in VHL.

Tuberous sclerosis complex (TSC) is a tumour predisposition syndrome associated with pathological variants in the TSC1 or TSC2 genes, which can lead to CNS hamartomas and subependymal giant cell astrocytomas, cutaneous angiofibromas, subungual fibromas, cardiac rhabdomyomas, pulmonary lymphangioleiomyomatoses, and renal angiomyolipomas. Approximately 4% of TSC patients will also develop renal cell carcinoma, predominantly of the chromophobe-like and papillary variants.
Here we present a pediatric patient with known TSC who developed a renal cortical lesion favoured to be a lipid-poor angiomyolipoma on radiological assessment. However, a biopsy of the lesion revealed a morphology suspicious for clear cell renal cell carcinoma, but with a focus of densely-packed pleomorphic cells amidst a background of fine, intricate vascular spaces, with unexpected immunopositivity for inhibin A. Upon external consultation, a diagnosis of clear cell renal cell carcinoma with hemangioblastoma-like change was rendered. This is an extremely rare morphological variant of clear cell carcinoma, with histomorphological features all-too-reminiscent of tumours more typically seen in VHL. As clear cell renal cell carcinoma is almost never seen in pediatric patients and not characteristically seen in TSC patients in general, this case represents both a radiological and pathological diagnostic pitfall.

Research theme 1: Cancer Biology
Research theme 2:
Research theme 3:

Presenter's Name: Win, Phyo

Additional Author(s): Lekhi M, Nguyen J, Arking D, Castellani CA

Abstract Title: Nuclear and mitochondrial DNA variation drive cardiovascular disease risk

Abstract:
Introduction: Cardiovascular disease (CVD) accounts for 17.9 million deaths globally each year. Mitochondria (mt) drives energy production and mt dysfunction is involved in atherosclerosis, the underlying cause of most CVD cases. Mt DNA variation influences the nuclear DNA (nDNA) epigenome. mtDNA copy number (mtDNA-CN), heteroplasmic mutations, haplotype, and haplogroup represent measures of mtDNA variation. mtDNA-CN is the number of mt genomes per cell, heteroplasmy is the ratio of mutated and wildtype mtDNA, haplotype describes polymorphic sets of nDNA that tend to be inherited together and haplogroups group similar haplotypes that share a common ancestor. All four categories of mtDNA variation have been found to be associated with CVD risk, but the mechanism remains unclear. We aim to characterize the extent by which nDNA methylation mediates the effect of mtDNA variation on CVD.

Methods: Prospective human cohorts including the Canadian Longitudinal Study on Aging (CLSA, N=26000) and the Atherosclerosis Risk in Communities (ARIC, N=12000) with available genomic (DNA microarray, whole genome sequencing (WGS)), and global epigenomic (microarray) data were used. mtDNA-CN, haplogroup, and haplotype were determined using the Axiom array and/or WGS. mtDNA heteroplasmy levels were obtained via WGS. nDNA methylation was called from the Infinium 450K and EPIC BeadChip arrays. Baseline and follow-up data was available for assessment of incident CVD outcomes.

Result: In ARIC individuals of European ancestry, 31 CpGs were found to be associated with heteroplasmy level (N=2114, P<1x10-7). In the CLSA, 738 and 88 CpG sites were identified to be significantly associated with global mtDNA haplogroup and haplotype variations, respectively (N=1336, P<1x10-7). Haplogroup L showed an associated risk with the development of peripheral vascular disease (N=26622, P=3x10-2). Further assessment of mtDNA features is ongoing. Gene ontology results revealed the cholecystokinin receptor binding (P=2x10-3) and guanyl-nucleotide exchange factor (P=3x10-4) pathways to be enriched in ARIC heteroplasmy and CLSA haplogroup analyses, respectively.

Discussion: mtDNA variation shows association with nDNA epigenetic variation, further highlighting nDNA methylation as a mediator between mtDNA variation and CVD. Elucidating the mechanisms driving these relationships will be critical for the development of approaches towards better diagnosis, treatment, and prevention of CVD.

Research theme 1: Bioinformatics and Data Science
Research theme 2: Cardiovascular, Respiratory Health, and Metabolic Diseases
Research theme 3: Epigenetics

Presenter's Name: Steriopoulos, Julia

Additional Author(s): Lu H, Chou M, Zhang Z

Abstract Title: The Molecular Mechanism of TLR3 Initiated Cell Death in Cardiac Allografts

Abstract:
Introduction: Apoptosis, necrosis, and necroptosis are the predominant forms of cell death involved during organ injury and damage, particularly in the case of transplantation. It was reported that RIPK1/RIPK3 will form complexes, known as necrosomes, which are necessary macromolecular structures in the execution of necroptosis after injury. As well, necroptosis related mitochondrial impairment has been shown to cause bioenergetic failure, generation of reactive oxygen species, and dysregulation of calcium homeostasis, which may prompt further necrosome formation and necroptosis. TLR3 has been shown to mediate apoptosis and necroptosis through its adaptor molecule TRIF, which is capable of binding RIPK1 or RIPK3, though the mechanism by which it does this is still uncertain. We aim to identify which molecules TRIF binds to when it directs cells down these pathways.

Methods: To test this hypothesis, we first treated cardiac microvascular endothelial cells (ECs) with synthetic dsRNA (Poly I:C) and a SMAC mimetic to induce cell death. IETD was used to direct the cells from an apoptotic to a necroptotic fate. Cell death was measured using a propidium iodide stain and imaging by the Cytation plate reader. We are in the process of collecting and running treated samples at various time points for co-immunoprecipitation of TRIF and its binding partner for protein detection. We will continue to use this workflow to elucidate the molecular cascade down to those leading to mitochondrial damage.

Results: Our results show that ECs will undergo apoptosis when stimulated with poly I:C and SMAC mimetic, and can be directed to a necroptotic fate by the addition of IETD. Death in cells directed towards apoptotic or necroptotic cell death can be prevented by the addition of RIPK1 inhibitor necrostatin. We have also found that TRIF is capable of binding RIPK1 and RIPK3.

Discussion: The ability of necrostatin to rescue cells from necroptotic death suggests that RIPK1 is involved in the necroptosis pathway in ECs. We will continue to investigate the extent of involvement of our molecules of interest following the methods previously described.

Research theme 1: Regenerative and Transplantation Medicine
Research theme 2:
Research theme 3:

Presenter's Name: Li, Xinru

Additional Author(s): Olea-Popelka F, Darling M

Abstract Title: Molecular Evaluation of Clinical Diagnosis of Oral Potential Malignant Disorders

Abstract:
Introduction: Oral potential malignant disorders (OPMDs) are a heterogeneous group of lesions and conditions characterized by an increased risk of transformation into oral squamous cell carcinoma (OSCC). Early detection is crucial as the majority of OSCC cases are detected at an advanced stage, with 5-year survival rate ranging from 40-50%. This study aims evaluate the accuracy of the clinical diagnosis of OPMDs using molecular methods to investigate oncogenic cellular pathways and the role of S100A7. S100A7 has been implicated as biomarker that might be predictive of malignant transformation of OPMDs.

Methods: A comprehensive molecular evaluation on biopsy samples from a cohort of patients clinically diagnosed with OPMDs was performed. RNA was extracted from formalin-fixed paraffin embedded tissues. A nanoString cancer immunology panel was selected to obtain a direct digital quantification of RNA expression levels of genes associated with oral carcinogenesis. Immunohistochemistry (IHC) was conducted to visualize the protein expression and localization of selected biomarkers; the slides were digitalized using Aperio slide scanner, and further analysis was done using QuPath software.

Results: Gene expression profiling showed elevated S100A7 expression in dysplasia lesions compared to normal oral mucosa. Notably, the overexpression of S100A7 was aligned with higher grades of dysplasia, indicating its potential as a biomarker for early detection of malignancy risk. Immunology pathways such as the complement and TNF superfamily pathways had elevated activation in dysplastic samples. Alterations in the the WNT and MAPK signaling pathways in OPMDs were also found. IHC staining of selected epithelial markers suggested epithelial-mesenchymal transition (EMT) in the OPMD cohort.

Discussion: The correlation of molecular data with clinical diagnoses provides a more comprehensive understanding of the malignant transformation potential of OPMDs. The identified molecular alterations offer promising targets for early intervention and risk prediction for patients with OPMDs. Future research should focus on longitudinal studies to validate these biomarkers as predictive tools for malignant transformation in OPMDs.

Research theme 1: Cancer Biology
Research theme 2: Digital Pathology
Research theme 3: Oral Biology and Medicine

Presenter's Name: Wang, Chao

Additional Author(s): Peng T

Abstract Title: Inhibition of histone deacetylases aggravates doxorubicin-induced injury in cardiomyocytes

Abstract: Background: Doxorubicin is widely used as an effective chemotherapeutic agent for many malignancies. However, the clinical application of doxorubicin is limited by its dose-dependent cardiotoxicity. Unfortunately, effective prevention and treatment are limited. Therefore, there is an urgent need to further understand the underlying mechanisms. Histone deacetylases (HDACs) are a class of enzymes comprising class I (HDAC1, 2, 3 and 8), class II (HDAC 4, 5, 6, 7, 9 and 10), class III (sirtuins), and class IV (HDAC11). Our previous study found that inhibition of classical HDAC (class I, II and IV) with Trichostatin A (TSA) enhanced doxorubicin-induced injury in cardiomyocytes. This study aimed to identify which member(s) of classical HDAC play a role in doxorubicin-induced cardiotoxicity.

Methods: Mouse neonatal cardiomyocytes were incubated with doxorubicin or saline in the presence of TSA (inhibitor for class I, II and IV HDACs), Apicidin (inhibitor for HDAC 2, 3 and 8), MS-275 (inhibitor for HDAC 1, 2 and 3), and PCI-34051 (inhibitor for HDAC 8) for 24 hours. Cell injury was determined by lactate dehydrogenase (LDH) release assay and cell viability was determined using cell counting kit-8 (CCK8) assay. Apoptosis was assessed by analyzing cleaved caspase-3 fragment by western blot.

Results: Incubation with TSA, Apicidin and MS-275 enhanced the release of LDH and further decreased cell viability in doxorubicin-stimulated cardiomyocytes. TSA also enhanced the levels of cleaved casepase-3 fragments induced by doxorubicin. In contrast, incubation with PCI-34051 did not change LDH release and cell viability in doxorubicin-induced cardiomyocytes.

Discussion: Our results suggest that HDAC2 and/or HDAC3 play a protective role in doxorubicin-induced injury in cardiomyocytes. Future study is needed to identify if HDAC2 or HDAC3 protects cardiomyocytes in doxorubicin-induced cardiotoxicity using their specific shRNA.

Research theme 1: Cardiovascular, Respiratory Health, and Metabolic Diseases
Research theme 2:
Research theme 3:

Presenter's Name: Tangri, Riya

Additional Author(s): Shooshtari P, Regnault TRH

Abstract Title: Genome-wide Meta-Analysis of the Human Placental Transcriptome in Association with Maternal Pre-pregnancy Body Mass Index

Abstract:
Introduction: An elevated maternal pre-pregnancy BMI is associated with adverse maternal and offspring outcomes, such as early pediatric NAFLD, insulin resistance and obesity. Altered maternal body composition is associated with changes in placental structure and function, which compromises the intrauterine environment and fetal development. However, the molecular mechanisms behind body composition associated placental changes are currently poorly understood.

Methods: To address the gaps in the literature, our study aimed to better understand how maternal pre-pregnancy BMI might be associated with an altered placental transcriptome. We conducted a genome-wide transcriptome meta-analysis, pooling together four pre-existing RNAseq datasets, to compare the mRNA expression profiles of underweight (n = 6), overweight (n = 40), and obese (n = 14) women with normal-weight women (n= 86). Univariate differential expression analysis was conducted using the DESeq2 package in R, with BMI used as both the continuous and categorical independent variable. The pathway analysis was completed using Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG).

Results: Our analysis showed a clear distinction in placental transcriptome between women of varying pre-pregnancy BMI. When compared to the normal weight women, there were 8 differentially expressed genes (BH-adjusted p-value < 0.05) for the underweight status, 58 differentially expressed genes (nominal p-value < 0.01) for the overweight status, and 123 differentially expressed genes (nominal p-value < 0.01) for the obese status. Pathway analysis identified the following key biological pathways and processes that were affected by maternal pre-pregnancy BMI in the placenta: nutrient transport, mitochondrial processes, oxidative stress, hormone activity, inflammation, and immune responses.

Conclusions: Our results suggest that maternal pre-pregnancy BMI affects biological processes from prenatal life onwards, and identifies placental molecular processes linking maternal body composition and fetal development, and subsequent postnatal health trajectories.

Research theme 1: Bioinformatics and Data Science
Research theme 2: Cardiovascular, Respiratory Health, and Metabolic Diseases
Research theme 3:

Presenter's Name: Syed, Urooj

Additional Author(s): Howlett C, Khan ZA

Abstract Title: Profiling bone marrow stem cell niche interactions in ageing

Abstract:
Introduction: The bone marrow niche serves as a vital microenvironment orchestrating interaction between various stem cell populations. While the niche has been extensively investigated, assessing the formation of micro-environments within the bone marrow regulated by growth factors and cytokines has proven difficult. The bone marrow niche's spatial organization, cellular makeup, and intercellular communication networks are crucial for regulating and maintaining tissue homeostasis. With aging, there's a dynamic shift in these interactions, leading to alterations in niche composition and function. Spatial heterogeneity in gene expression highlights the importance of niche architecture in regulating stem cell behaviour.

Methods: To examine cellular changes in the bone marrow, tissue samples were obtained from the tibia and femur of C57BL/6 mice from age points between 8 weeks to 71 weeks. Tissue samples will be subjected to immunohistochemical staining to visualize resident stem cells expressing Sca-1 and Sox2 expression markers. Subsequently, Sca-1 positive cells will be isolated via flow cytometry for comprehensive analysis of their stem cell properties. RNA-sequencing analyses will be conducted to determine differential gene expression patterns within the niche components of aged mice. Additionally, Visium Spatial Gene Expression will be used to map the spatial distribution of cell types and their gene expression patterns within the marrow.

Results: This study is currently ongoing. We have obtained bone tissues from mice and begun optimizing Sca-1 and Sox2 antibodies. We have revealed Sox2 expressing stem cells in positive controls of human lung and GBM tissues. Based on previous studies, We anticipate that aged bone marrow niches will exhibit diminished complexity and altered cellular composition, characterized by reductions in niche-supporting cell populations and dysregulation of niche signalling pathways. We predict that these changes will disrupt the spatial organization of the bone marrow niche, impairing stem cell maintenance and self-renewal capacities

Discussion: Our hypothesized findings hold the potential to provide novel insights into the functional consequences of altered signalling in aged HSCs. Understanding the intricate interplay between stem cells and their niche is essential for developing targeted interventions to counteract age-related declines in hematopoietic function and tissue regeneration.

Research theme 1: Cancer Biology
Research theme 2: Infection, Immunity, and Inflammation
Research theme 3: Regenerative and Transplantation Medicine

Presenter's Name: Lopes, Alana

Additional Author(s): Rasmussen S, Au R, Chinnery T, Christie J, Djordjevic B, Gomez JA, Grindrod N, Policelli R, Sharma A, Tran C, Walsh J, Wehrli B, Ward AD, Cecchini M.

Abstract Title: Exploring the Non-Medical Application of Pathologists' Visual Search Skills

Abstract:
Introduction: The digital revolution of pathology has fostered new research areas like the detailed study of pathologists' visual search patterns. This study used eye tracking technology to determine if pathologists' training translates to a non-domain specific search task, and whether pathologists perform this search task differently from laypeople and differently than they perform a domain specific search task.

Methods: Six pathologists were recruited as observers and six graduate students were recruited as lay observers. The non-domain specific task had all observers search for Waldo in 5 "Where's Waldo?" puzzles. The domain specific task had pathologists search for a single mitotic figure in 5 digital breast pathology slide images. Observers' eye gaze data were collected using the Tobii Pro Fusion eye tracker. False negative rate (FNR), when the observer misclassified the target of their fixation, was recorded. Linear discriminant analysis (LDA) was used to find the one-dimensional representation that best separated the observer groups based on their fixation and saccade rate, gaze transition entropy, and median fixation duration, saccade amplitude, peak saccade velocity, and image area covered by and overlapped with fixations.

Results: There was no significant difference between pathologists and laypeople for FNR. Pathologists' median fixation rate was 3.17/s vs. 2.61/s for laypeople ($p<0.0001$). Saccade rate was 2.77/s for pathologists vs. 2.47/s for laypeople ($p<0.0001$). Median gaze transition entropy was equivalent amongst both groups. Pathologists had shorter median fixation durations (244ms) than laypeople (300ms, $p<0.0001$). Median saccade amplitude of pathologists was 1.47 vs. 1.40 for laypeople ($p=0.60$). Pathologists' peak saccade velocity was 82.1 /s vs. 77.8 /s for laypeople ($p=0.02$). No significant difference was found between the two cohorts for image area covered by and overlapped with fixations. Pathologists' scan paths differed from those of laypeople with an LDA misclassification rate of 10.2%. Further, pathologists' scan paths for Waldo vs. mitotic figures differed with a 0% LDA misclassification rate, indicating the scan paths were fully separable.

Discussion: Pathologists' training does not improve accuracy in non-domain search tasks but does improve the speed of both their search and classification, without affecting FNR. This implies pathologists can rapidly classify the objects of their fixations without compromising accuracy.

Research theme 1: Digital Pathology
Research theme 2:
Research theme 3:

Presenter's Name: Hayes, Charlotte

Additional Author(s): Ettler HC, Chan NG, Goebel EA

Abstract Title: Reasons for Submission of Placentas to Pathology: A Review with Diagnostic Correlation and Estimation of Clinical Impact

Abstract:
Introduction: There are more than 6000 births at LHSC annually and a large number of placentas are submitted for pathologic examination. The submission policy is broad and states "any placentas associated with any abnormal pregnancy events or outcome should be submitted for examination." There is often a delay in reporting placentas, as these are not prioritized in the pathology department. In addition, the overall number of clinically significant diagnoses is unknown. The objective of this study is to summarize and analyze the reasons for submission and pathologic examination of placenta cases previously submitted to LHSC Pathology, and evaluate the need for more specific placenta submission guidelines.

Methods: All placenta pathology reports from January to December 2021 were retrieved from the LHSC pathology database and retrospectively reviewed. The cases were categorized according to reason for submission (RFS) and pathological diagnosis. Turn-around-time (TAT) from the day the placenta was submitted to pathology to the day the pathology report was issued was determined. Results: 1369 placenta pathology reports were retrieved. The average TAT for issuing a pathology report was 36 days (range of 2 to 97 days). The top three RFS were intrauterine growth restriction, preterm/premature birth and chorioamnionitis. 256 cases (19%) had no pathological findings and several others had only focal/minor findings. Pathologic examination confirmed chorioamnionitis in 84% of cases, when it was the RFS. Only 2 cases (0.15%) were submitted for reasons not covered in the LHSC specimen submission policy.

Discussion: The placenta submission guidelines are broad. Almost one fifth of submitted cases had no pathologic findings and therefore are presumed to have no clinical impact. Others, with only minor findings, are unlikely to have clinical impact, especially when coupled with a long TAT. Furthermore, when the RFS was chorioamnionitis, placental examination did not always confirm the diagnosis; even with this significant diagnosis the patient likely would have been treated before the report was issued, thereby reducing the clinical impact of the pathology report. Next steps include surveying Obstetricians on the clinical impact of placenta pathology reports and using that in conjunction with the data from this study to potentially refine placenta submission guidelines, which in turn may reduce pathology workload and improve TAT without negatively impacting patient care.

Research theme 1: Test Utilization, Optimization and Quality Assurance
Research theme 2:
Research theme 3:

Presenter's Name: Rudak, Patricia

Additional Author(s): Truong I, Cecchini M

Abstract Title: Development and Evaluation of a Novel Tile-based Digital Image Classification Application for Continuing Professional Development in Pathology

Abstract:
Introduction: The process of identifying biomarkers is growing more complicated, highlighting the need for enhanced tools to aid pathologists in accurately reporting these markers. Particularly, the task of assessing PD-L1, presents significant difficulty for pathologists due to the complexity of its scoring system and the variability in results between different observers. This project introduces a novel technology tool for pathologist training through the scoring of histologic head and neck, and gastrointestinal image tiles. These labelled tiles can then be utilized to support machine learning algorithms that can act as an adjunct to human assessment.

Methods: Pathologists and residents will be evenly split into two different training strategies using block randomization, ensuring an equal number of participants in each group throughout the study. The first group will learn by reviewing digital slides and then classifying diseases and rating their diagnostic confidence on a scale from 0 to 100%. The second group will use our new tile-based training application to prepare for their tasks. The random assignment is generated by a computer algorithm and is structured in blocks of four to maintain balance in the allocation.

Results: The tile-based training application incorporates a large set of anonymized, digitized pathology slides that have been meticulously segmented into tiles via QuPath software to simulate what pathologists see under a microscope. These tiles have been integrated into a digital platform for preliminary testing, which presents them in a random order to participants where participants are prompted to enter an integer value corresponding to the combined positive score or mark the sample as 'insufficient' should there not be enough cells to evaluate.

Conclusion: Initial results indicate that this approach may offer a more consistent and reliable method for pathologists to evaluate complex biomarkers, potentially reducing variability in diagnosis and enhancing the overall quality of patient care.

Research theme 1: Digital Pathology
Research theme 2:
Research theme 3:

Poster Presentations
Session 2
10:45 a.m. - 12:00 p.m.

#	First Name	Last Name	Title
1	Richard	Zhang	Identifying shared and distinct gene regulatory mechanisms across 8 different psychiatric disorders
2	Kelli	Wang	Targeting Fibrotic Pathways: The Anti-Scarring Potential of Losartan Following Glaucoma Surgery
3	Serina	Chahal	Impact of Circular RNA ZMIZ1 Silencing on Dendritic Cell Activity and Immune Regulation
4	Parsa	Khanderooy	Evaluation of Targeted Next-Gen Sequencing and Chromosomal Microarray Analysis for detection of Copy Number Variants in Solid Tissue samples of Gliomas
5	Nelson	Chang	Islet Paracrine Factors Direct Glucagon to Lysosomes in Pancreatic Alpha Cell
6	Michael	Chou	Determining the Molecular Mechanism of Signaling Between the Necrosome and Mitochondria During TLR-3-Mediated Necroptosis
7	Venkat Vaibhav	Mani Murugan	The role of 5-lipoxygenase (5-LO) expressing cells in colitis-associated colorectal cancer

#	First Name	Last Name	Title
8	Amir Hossein	Karimi	TIM3 as a Modulator of the Immune Microenvironment in Head and Neck Squamous Cell Carcinoma: The Prognostic Potential and the Therapeutic Implications
9	Josh	Del Papa	Perineural inflammation as a novel feature in lichen sclerosus; a case series of histological and clinical features
10	Lianna	Kruger	The Sound of Pathology
11	Meggie	Vo	Mitochondrial ROS-induced SerpinA3 expression protects cardiomyocytes against Doxorubicin-induced injury
12	Amanda	Liddy	Enhancing anti-tumor and gut microbial responses to anti-PD1 immunotherapy through Akkermansia muciniphila supplementation in pancreatic cancer
13	Xuan	Wang	Characterizing the Amygdala Involvement in Sudden Unexpected Death in Epilepsy: A Pathology and MRI Correlation Study
14	Karshana	Suthakaran	Examining the Impact of Environmental Enrichment on Autism Spectrum Disorder Through the Use of Cntnap2 Knockout Model Rats
15	Muhammad	Sulman	Quantitative analysis of eplet load in heart transplant success: Evaluating the significance of mismatches across different HLA loci
16	Eric	Liu	A deep active learning framework for mitotic figure detection in Glioblastoma histology images
17	Natasha	Holder	Glandular Odontogenic Cyst: Molecular Analysis using Targeted Next-Generation Sequencing
18	Jingwen	Yang	Determining the interaction between junctophilin-2 and junctin by the BiFC assay
19	Aparna	Sreeram	Association Between Enhanced Adipogenesis and Diabetic Neuropathy in Bone Marrow
20	Lauren	Volcko	Facilitators and Barriers of Implementing Digital Interventions for Diabetes: A Scoping Review
21	Daniel	Kawa	Characterizing p66Shc-Dependent Effects on Pluripotent Stem Cell Fate Using Teratomas for Comparative in vivo Multi-Lineage Differentiation Modeling

#	First Name	Last Name	Title
22	Tiffany	Cheung	Changes in Systemic Cytokine Levels from Gut Microbiota Modulation with Antibiotics and Immunotherapy
23	Kevin	Feng	Predictive Modeling of Kidney Stone Composition Using Machine Learning and Clinical Data
24	Ashley	Faulkner	Assessing the concordance of gross and microscopic margins in pancreatic cancer resections: a retrospective cohort study from January 2013 to December 2022
25	Jennifer	Coats	Analysis of tumor cellularity variance in simulated core needle biopsy specimens across resected lung cancer cases.
26	Justin	Donovan	Enhanced detection of SARS-CoV-2 variants through wastewater surveillance: Insights for public health preparedness
27	Ginnian	Leung	The effects of EZH2 inhibition on colitis-associated colorectal cancer initiation
28	Isabella	Monaghan Chow	Identification and Characterization of circCRIM1 expression profile in Cardiomyocytes

#	First Name	Last Name	Title
29	Haley	McConkey	Diagnostic utility of DNA methylation episignature analysis for early diagnosis of KMT2B-related disorder: case report form national EpiSign-CAN trial
30	Pious	Jose	Exploring Epigenetic Age Acceleration and Mitochondrial Dysfunction in Asthma
31	David	Charrette	Expression of S100A7 in Soft Palate Dysplasia and Maxillectomy Margins.
32	Michael	Roes	A genome-wide CRISPR screen reveals TBX18 loss as a novel driver of enzalutamide resistance in prostate cancer
33	Abigail	Whittier	Validation of the Roche Epstein-Barr virus serology assays
34	Leina	Burley	Investigation of Metabolic Pathway Use by Th2 vs Th2-Th17 Cells
35	Louise	Mui	Examining the Concordance of Hereditary Cancer Gene Mutations between Normal Tissue, Tumor, and Germline Testing in Patients with High Grade Serous Ovarian Carcinoma
36	Nader	Shaker	S100A7 expression in oral potentially malignant disorders: verrucous hyperplasia and verrucous carcinoma

#	First Name	Last Name	Title
37	Maria	Daniel	Exploring the Role of the Adaptor Protein p66Shc on Murine Embryonic Stem Cell Differentiation and Maturation
38	Hazeema		Bridging the Gap: Insights from a Scoping Review on Reducing Hypertension Control Disparities in Primary Care Settings
39	Trinity	Quan	Developing a Histopathological Atlas of Laboratory Mouse Tissues as an Open Educational Resource
40	Gwendolyn	Conant	Introduction to grossing using standardized simulated specimen models
41	Timothy	Nunes	Lifelong maternal Western Diet negatively impacts placental metabolome and placental vascularization, independent of BMI
42	Kevin	Vytlingam	Preventing Alloimmune Rejection After Heart Transplantation Using Circular RNA ZMIZ1-Engineered Dendritic Cells
43	Carolyn	Twible	Characterizing hippocampal dentate gyrus involvement in temporal lobe epilepsy

#	First Name	Last Name	Title
44	Elissa	Woo	Comparison of digital image analysis and light microscopy for identification of HER2-low breast cancer
45	Zoya	Khandwala	The role of the WNT signalling cascade on Epithelial-Mesenchymal Transition in High-Grade Serous Ovarian Cancer
46	Ji Hyun	Han	Osteomyelitis of the jaw: An investigational study of the clinicopathological features and pathogenesis of refractory vs non refractory osteomyelitis
47	Ivy	Truong	Optimizing the digital quantification of PD-L1 as a predictive marker for immunotherapy response
48	Jenna	Orsava	The Interplay of Piezo1 and DLC1β in Cardiac-Ischemia Reperfusion Injury During Heart Transplantation
49	Janice	Sutherland	A Qualitative Examination into the Factors that Influence Dog Walking: A One Health Approach
50	Haitao	Lu	The ZBP1-RIPK3 complex orchestrates PANopotosis to induce cell death and transplantation rejection by sensing cfDNAs

Presenter's Name: Zhang, Richard

Additional Author(s): Hosseini N, Shooshtari P

Abstract Title: Identifying shared and distinct gene regulatory mechanisms across 8 different psychiatric disorders

Abstract:
Introduction: The pathophysiology underlying psychiatric disorders and the shared/distinct mechanisms between them are not well understood. To date, several genome-wide association studies (GWASs) have found tens to hundreds of genomic loci associated with psychiatric disorders. Most of the disease risk variants (i.e., SNPs) found by these GWASs lie in regulatory regions, specifically open chromatin sites in brain cell types. To investigate the gene regulatory effects of these SNPs, an integrative analysis of GWAS and single cell ATAC-seq (scATAC-seq) data can be performed. Previous data integration studies mainly focus on one disease, and a comprehensive comparison across multiple diseases is lacking. We aimed to integrate 11 psychiatric GWAS datasets, encompassing 8 disorders, with 3 brain scATAC-seq datasets, to test the hypothesis that shared/distinct cell type-specific gene regulatory mechanisms across psychiatric disorders can be found through a data integration approach.

Methods: We obtained GWAS results for 8 psychiatric diseases from the Psychiatric Genomics Consortium, GWAS Catalog, and PubMed. We used 3 scATAC-seq datasets containing cell types from the developing human and mouse brain, and adult human brain. A data integration pipeline developed at the Shooshtari lab, incorporating standard R packages and command line tools, was used to integrate GWAS and scATAC-seq data. Our pipeline prioritized SNPs, cell type and developmental stage-specific open chromatin peaks, transcription factors, and genes relevant to each disease. We identified pertinent pathways using common pathway analysis tools, GREAT and EnrichR. Finally, we compared results across the 8 disorders.

Results: Our analysis found a median of 340 SNPs influencing TF binding, 46 open chromatin peaks, 54.5 TFs, and 14 genes associated with each psychiatric disease. A total of 52 biological pathways were linked with at least one disorder. Notably, the TFs ETV3 and DLX6 were each prioritized in 4 different psychiatric disorders. The gene TMEM106B was linked to Alzheimer's disease, depression, and anxiety. Additionally, three genes (SMG6, FAM53C, and CDC25C) were found relevant to both schizophrenia and bipolar disorder.

Discussion: Our findings support the results of previous studies which proposed relationships between groups of psychiatric disorders, and the roles of specific genes, TFs, and pathways in different disorders, while providing novel insights into disease mechanisms.

Research theme 1: Bioinformatics and Data Science
Research theme 2: Epigenetics
Research theme 3:

Presenter's Name: Wang, Kelli

Additional Author(s): Li G, Vinokurtseva A, Teplitsky JE, Liu H, Hutnik CML

Abstract Title: Targeting Fibrotic Pathways: The Anti-Scarring Potential of Losartan Following Glaucoma Surgery

Abstract:
Introduction: Glaucoma is the leading cause of irreversible blindness, affecting over 80 million individuals worldwide. It refers to a spectrum of optic neuropathies of which the only modifiable risk factor is intraocular pressure, and surgery is the most definitive way to lower it. The surgery creates an alternative drainage pathway for fluid, thereby reducing the risk of glaucomatous progression. Unfortunately, excessive post-surgical subconjunctival scarring driven by Human Tenon's capsule fibroblasts (HTCFs) results in surgical failure by blocking the newly created drainage pathway. Mitomycin C is the current gold-standard treatment for postoperative scarring, but it exhibits unreliable effectiveness and causes many adverse effects. Safer, more effective, and more predictable ways to modulate post-surgical wound healing would be a major advancement. Exploring the off-target effects of therapeutic agents that are already used represents a novel approach to drug discovery. Angiotensin receptor blockers (ARBs) are oral medications widely used to treat systemic blood pressure. This research explores the potential of ARBs when administered in the eye, to downregulate TGFβ1 induced HTCF myofibroblast transdifferentiation through modulation of the renin-angiotensin system. The aim of this study is to assess the anti-fibrotic effects of losartan (LS), an ARB, on HTCFs in an in vitro model.

Methods: Optimal concentrations of both LS and Angiotensin I (AngI) were determined by creating a dose-response curve using assays of cellular metabolic activity (MTT) and cell death (LDH). Primary cultures of HTCFs generated from glaucoma patients were pre-treated with 2, 20, or 40 μM of LS for 24h, then 0.1 or 100 μM of AngI for 48h. When the appropriate treatment concentrations are determined, Western blot and immunofluorescence assays will be performed to examine the anti-fibrotic effects of LS.

Results: The optimized LS concentration of 20 μM decreased cell metabolism, while having minimal effect on cytotoxicity. Meanwhile, the optimal AngI concentration was 0.1μM and caused an increase in cellular metabolic activity with little effect on cytotoxicity.

Discussion: The behaviour of HTCFs when exposed to LS and AngI supports the potential for LS to be further explored as a wound modulating agent. Further experiments aimed at investigating the effects on pro-fibrotic proteins such as αSMA and MMP-9 will provide premise to explore this novel off-target effect of LS.

Research theme 1: Cardiovascular, Respiratory Health, and Metabolic Diseases
Research theme 2:
Research theme 3:

Presenter's Name: Chahal, Serina

Additional Author(s): Li S, Zheng X

Abstract Title: Impact of Circular RNA ZMIZ1 Silencing on Dendritic Cell Activity and Immune Regulation

Abstract:
Introduction: Dendritic cell (DC)-based vaccines for cancer immunotherapy have shown great promise in the past; however, optimization of DC function is necessary to increase therapy efficacy. Recently, circular RNAs have been shown to be differentially expressed between tolerogenic versus inflammatory, immunogenic DCs. Our study examines the role of circular RNA ZMIZ1 (circZMIZ1) and its role in DC function, where we aim to demonstrate that circZMIZ1 is immunosuppressive, and that silencing of circZMIZ1 can promote the production of inflammatory, immunogenic DCs, resulting in increased activation of T cell immune responses.

Methods: Bone marrow-derived DCs were treated with immune modulating small molecules and circZMIZ1 siRNA in vitro. The expression of circZMIZ1, PD-L1 and cytokines were measured using qRT-PCR. DC phenotype was determine using flow cytometry. For in vivo expression, DCs were isolated from the secondary lymphoid organs of mice bearing EO771 breast tumours and wild-type mice.

Results: CircZMIZ1 shows a positive correlation with PD-L1 expression both in vitro and in vivo. In vivo, circZMIZ1 expression is increased in tolerized DCs isolated from EO771 breast tumour-bearing mice relative to WT mice. Silencing of circZMIZ1 in DCs is shown to decrease the expression of PD-L1, while conversely increasing the percentage of CD80+CD40+ immunogenic DCs. The IL-12/IL-10 cytokine ratio is also increased after circZMIZ1 silencing, indicating increased DC immunogenicity. We have found circZMIZ1 to interact with the JNK1 kinase, a known regulator of PD-L1 in other cell types. We expect siRNA-mediated silencing of circZMIZ1 to decrease PD-L1 expression through inhibition of JNK1's activity in DCs, resulting in their increased capacity to activate inflammatory T cells and restrict tumour growth.

Discussion: Here we propose the circZMIZ1–DC axis as a novel regulator of DC function, providing insight on how DCs can be optimized for use in immunotherapeutic treatment of immune dysfunction diseases.

Research theme 1: Infection, Immunity, and Inflammation
Research theme 2:
Research theme 3:

Presenter's Name: Khanderooy, Parsa

Additional Author(s): Lalonde E, Mohseni Meybodi A

Abstract Title: Evaluation of Targeted Next-Gen Sequencing and Chromosomal Microarray Analysis for detection of Copy Number Variants in Solid Tissue samples of Gliomas

Abstract:
Introduction: The detection of copy number variants (CNVs) plays a pivotal role in the diagnosis, subtyping, and treatment of gliomas. While Fluorescent In Situ Hybridization (FISH) remains the clinical gold standard for CNV diagnosis, its utility is limited by lengthy processing times, the necessity for manual analysis, and the need for experienced personnel. Emerging technologies such as Next-Generation Sequencing (NGS) and Chromosomal Microarray Analysis (CMA) have shown promise for CNV detection. Our study seeks to evaluate the accuracy of NGS and CMA in identifying key glioma CNVs, including EGFR amplification, 1p19q Co-deletion, Monosomy 10, Trisomy 7, and the homozygous deletion of CDKN2A/B genes compared to FISH in FFPE glioma tissues.

Methods: This study involved a retrospective review of patient charts and test results to select appropriate FFPE specimens. We assessed CMA accuracy using 16 glioma specimens previously analyzed by FISH and microarray between 2021 and 2023. For NGS accuracy, we examined 21 specimens analyzed by FISH and NGS from 2021 to 2023, with 10 samples having undergone all three analyses. FISH served as the reference standard. We utilized the Oncomine Comprehensive Assay v3 (OCA v3) (Thermo Fisher Scientific, USA) for targeted NGS, complemented by Ion Reporter for software analysis, and developed a custom pipeline for additional CNV detection.

Results: Preliminary CMA results demonstrated variable accuracy across different CNVs. Detection of 1p deletion yielded concordant results in 13 of 14 cases (92.86%). Detection of CDKN2A/B homozygous deletion, EGFR amplification, Trisomy 7, and Monosomy 10 was 100% concordant. However, only one of seven positive cases for 19q deletion was identified. Analysis from targeted NGS is in progress, with expectations for high accuracy in identifying the relevant CNVs.

Discussion: This study underscores the potential of integrating high-throughput technologies like NGS and CMA into clinical practice, potentially replacing FISH. Such advancements could significantly reduce diagnostic turnaround times for glioma CNVs from months to weeks, especially critical in regions facing shortages of medical laboratory technologists. However, the adoption of these methods requires standardization and the establishment of custom reference baselines for comparison. Our findings will contribute to the standardization efforts for CNV detection in FFPE samples using targeted NGS and CMA.

Research theme 1: Cancer Biology
Research theme 2: Test Utilization, Optimization and Quality Assurance
Research theme 3:

Presenter's Name: Chang, Nelson

Additional Author(s): Dhanvantari S, Madahey H

Abstract Title: Islet Paracrine Factors Direct Glucagon to Lysosomes in Pancreatic Alpha Cell

Abstract:
Introduction: Under physiological conditions, alpha cells of the pancreatic islets secrete glucagon in response to low blood glucose levels to maintain glucose homeostasis. In diabetes, glucagon secretion becomes unregulated and abnormally high (hyperglucagonemia), which may contribute to diabetes progression. Our lab has identified proteins that control glucagon secretion as possible targets for the treatment of diabetes. In particular, we identified a novel protein, Stathmin2 (Stmn2) in TC1-6 cells that inhibits glucagon secretion by directing glucagon trafficking to lysosomes. We are now investigating whether inhibition of glucagon secretion by the islet paracrine factors insulin and somatostatin operates through the Stmn2-mediated lysosomal pathway. In the present study, I hypothesize that insulin and somatostatin inhibit glucagon secretion via the Stmn2-mediated lysosomal pathway and the its disruption results in excess secretion seen in diabetes.

Methods: AlphaTC1-6 cells were treated with paracrine factors and stained with exocytosis (Syntaxin-1A) and lysosomal markers (LAMP1) to visualize intracellular trafficking of glucagon by confocal microscopy. Stmn2 was overexpressed and silenced to visualize changes in the fluorescence intensity and distribution of lysosomes to examine Stmn2's regulatory mechanism. Nuclear translocation of transcription factor involved in lysosomal biogenesis was also assessed to determine the level Stmn2 functions at.

Results: Our results showed that insulin and somatostatin decrease glucagon colocalization in the cell periphery where exocytosis occurs and an increase glucagon colocalization with the lysosomal marker in these alpha cells. In addition, Stmn2 overexpression increases nuclear translocation of transcriptional factor and expression of genes involved in lysosomal biogenesis. Live-cell imaging also showed a distinct distribution pattern of lysosomes in Stmn2 knockdown and overexpression.

Discussion: These results suggest that the lysosomal network is sensitive to paracrine factors, as a mechanism in which glucagon secretion is regulated in these alpha cells. In addition, increased expression of genes involved in lysosomal biogenesis upon Stmn2-overexpresion, as well as increased degradative lysosomal signal suggest Stmn2's role in the lysosomal network at the transcriptional level, validating its potential as a target for hyperglucagonemia regulation of diabetes.

Research theme 1: Cardiovascular, Respiratory Health, and Metabolic Diseases
Research theme 2: Pathobiology of Neurologic Diseases
Research theme 3:

Presenter's Name: Chou, Michael

Additional Author(s): Steriopoulos J, Lu H, Zhang Z

Abstract Title: Determining the Molecular Mechanism of Signaling Between the Necrosome and Mitochondria During TLR-3-Mediated Necroptosis

Abstract:
Introduction: Organ rejection continues to be a major challenge in the field of transplant medicine. Cell death pathways such as necroptosis contribute to this rejection, but the mechanism of necroptosis is not well understood. More specifically, the molecular mechanism of the pathway between the mitochondria and necrosome is currently unknown during toll-like receptor 3 (TLR-3)-mediated necroptosis. We hypothesize that phosphoglycerate mutase 5 (PGAM5) and dynamin-related protein 1 (Drp1) are used by the necrosome to signal to the mitochondria during TLR-3-mediated necroptosis. We also hypothesize that PGAM5 and Drp1 are directly recruited by the necrosome during TLR-3-mediated necroptosis, rather than through an intermediate signaling molecule.

Methods: PGAM5 and Drp1 in microvascular endothelial cells (MVECs) will be silenced by PGAM5 or Drp1 siRNAs and necroptosis will be induced to determine if there is a significant decrease in cell death. Co-immunoprecipitation will then be done in control MVECs to determine if PGAM5 and Drp1 are directly recruited and bound to the necrosome.

Expected Results: We expect PGAM5 and Drp1-silenced MVECs to exhibit significantly less necroptosis than control cells. This means that when compared to control cells, PGAM5 and Drp1 silenced MVECs should exhibit a significantly lower level of cell death. In addition, through co-immunoprecipitation, we expect to find that PGAM5, Drp1, and the necrosome directly interact by binding to each other.

Discussion: These expected findings would provide evidence for the involvement of PGAM5 and Drp1 in the TLR-3 necroptosis pathway, as well as the potential pathway in which PGAM5 and Drp1 are involved. Given that organ rejection is one of the leading causes of death after an organ transplant, defining the TLR-3 necroptosis pathway will help future researchers develop new therapeutic strategies to target necroptosis in the cells of newly transplanted organs. This can help overcome the challenge of organ transplant rejection and further advance the knowledge in the field of transplant medicine.

Research theme 1: Regenerative and Transplantation Medicine
Research theme 2:
Research theme 3:

Presenter's Name: Mani Murugan, Venkat Vaibhav

Additional Author(s): Zhang L, Pallister M, Asfaha S

Abstract Title: The role of 5-lipoxygenase (5-LO) expressing cells in colitis-associated colorectal cancer

Abstract:
Introduction: Patients with prolonged ulcerative colitis (UC) exposure are 20% more likely to develop colorectal cancer (CRC). Tuft cells, a rare epithelial cell type within the intestinal crypt, may be the origin for colitis-associated cancer (CAC). To study this, I will be working with a new transgenic mouse model 5-LO-GFP-DTR-CreERT2 mice, wherein tuft cells are marked by 5-lipoxygenase (5-LO) expression. 5-LO expression is also seen in macrophages, which has been shown to play a role in tumorigenesis. The transgenic construct also contains GFP for detection by microscopy, DTR for selective cell ablation, and CreERT2 for conditional expression. Due to the abundance of genetic tools, this can be an effective mouse model for studying CAC.

Methods: 1) Characterize the location and expression profile of 5-LO+ cells within the intestinal epithelium and bone marrow for all three mouse lines. Immunofluorescent staining of the colon and bone marrow (BM) was conducted to quantify the number of GFP+ cells per 100 crypts across the rectum, distal colon, and proximal colon. 2) Determine whether 5-LO+ epithelial cells give rise to colitis-associated CRC. 5-LO-GFP-DTR-CreERT2 mice crossed to APC fl/fl mice were treated with three doses of 6mg tamoxifen, followed by five days of 2% DSS to induce colitis. 14 weeks following DSS treatment, the mice were sacrificed for histology, tumor number and size.

Results: Immunofluorescent staining of the colon and BM shows frequent endogenous GFP fluorescence with 7 GFP+ cells per 100 crypts and 15% of total cells, respectively. For the tumor experiments, two tumors were generated (n=4) and verified through histology. The tumor-bearing mice will be analyzed further to optimize the protocol for tumor generation.

Discussion: With the highest number of GFP+ cells observed in the colon of Line 3 mice, it could be the most effective of the three mouse lines at studying CAC. High GFP+ labelling in the BM of Line 3 mice also opens the door for future BM transplant experiments to investigate the role of macrophages in CAC.

Research theme 1: Cancer Biology
Research theme 2: Infection, Immunity, and Inflammation
Research theme 3:

Presenter's Name: Karimi, Amir Hossein

Additional Author(s): Shaikh MH, Zeng PYF, Barrett JW, Nichols AC

Abstract Title: TIM3 as a Modulator of the Immune Microenvironment in Head and Neck Squamous Cell Carcinoma: The Prognostic Potential and the Therapeutic Implications

Abstract:
Introduction: The incidence of head and neck squamous cell carcinoma (HNSCC) is increasing worldwide. Although current treatment paradigms carry significant morbidity, survival remains suboptimal. We have previously shown that HNSCC patients with a lower intensity of immune infiltration and poorer survival exhibited elevated expression of the immune checkpoint receptor TIM3. Accordingly, we hypothesized that TIM3 functions as a key regulator of the immune response in HNSCC and may serve as a prognostic marker and a druggable target for therapeutic intervention specifically in the context of combination therapy with anti-PD1 antibodies.

Methods: The TCGA-HNSC RNA-seq dataset was used to assess the association of TIM3 expression with prognosis. MCPcounter was applied to estimate the abundance of T-cell infiltration in the samples, and Cox regression was utilized to evaluate the prognostic potential of TIM3 while accounting for the potential confounding factors. The efficacy of TIM3 inhibition on the suppression of tumour growth was assessed using syngeneic mouse models of both human papillomavirus positive (HPV+) and HPV- HNSCC. The engrafted mice were randomized into four arms receiving either the isotype-control, anti-PD-1 antibody, anti-TIM3 antibody, or the combination of anti-PD1 and anti-TIM3 antibodies and were monitored for tumour growth. Flow cytometry, immunohistochemistry, and single-cell RNA-seq were used to mechanistically explore the effects of the treatments.

Results: Survival analysis revealed that the expression of TIM3 is an independent predictor of patient survival (p-value < 0.001) while accounting for the effects of T-cell infiltration, age, sex, the history of smoking and alcohol abuse, tumour anatomical subsite, and the AJCC clinical staging. Moreover, the combination of PD1 and TIM3 inhibition significantly decreased the rate of tumour growth in both HPV+ and HPV- syngeneic models (p-value < 0.01). Furthermore, single-cell RNA-seq revealed the functional effects of anti-TIM3 treatment on the tumour microenvironment.

Discussion: Collectively, these results indicate that the expression of TIM3 is a candidate prognostic marker in HNSCC and that combination therapy with anti-TIM3 and anti-PD1 antibodies is a prospective strategy to improve HNSCC patient outcomes. A window of opportunity clinical trial by our team is already underway to investigate the clinical benefits of the combination therapy in the neoadjuvant setting.

Research theme 1: Bioinformatics and Data Science
Research theme 2: Cancer Biology
Research theme 3:

Presenter's Name: Del Papa, Josh

Additional Author(s): Pucchio AC, Schneider M, Wang A

Abstract Title: Perineural inflammation as a novel feature in lichen sclerosus; a case series of histological and clinical features

Abstract:
Lichen sclerosus is a frequently encountered inflammatory skin disorder characterized by whitened, atrophic patches that can cause pain and pruritis. The underlying cause of this condition remains unknown. Primarily affecting the genital area, this condition carries an increased risk of developing cutaneous cancers and frequently co-occurs with autoimmune disorders. Our retrospective study aimed to explore histological features of lichen sclerosus, with a particular focus on a newly established finding and its potential implications.

We examined 53 histological cases of lichen sclerosus collected over two years. Experienced pathologists evaluated and reached a consensus on the assignment of histological features. Patient charts were manually reviewed to gather relevant demographic and clinical data. Statistical analysis was performed using IBM SPSS Statistics (2021).

Of the 53 total patients identified as meeting criteria for inclusion in this study, only eight (15%) were male. Eight cases (15%) demonstrated perineural inflammatory infiltrate. Notably, half of all samples from male patients exhibited perineural inflammatory infiltrate. A statistically significant increase ($p<0.01$) in the presence of dermal plasma cells was identified in cases with perineural inflammation vs. cases without this feature.

Our study's findings highlight the recurrent nature of perineural inflammation in lichen sclerosus, providing valuable insights into this condition. Furthermore, we observed a notable correlation between perineural inflammation, male patients, and the presence of dermal plasma cells. These discoveries contribute to a better understanding of the underlying mechanisms of lichen sclerosus and suggest avenues for future research into the condition.

Research theme 1: Infection, Immunity, and Inflammation
Research theme 2:
Research theme 3:

Presenter's Name: Kruger, Lianna

Additional Author(s): Grindrod N, Cecchini M

Abstract Title: The Sound of Pathology

Abstract:
Introduction: Digital pathology is rapidly evolving the way cancer patients are diagnosed. One of the greatest challenges that pathologists face is the identification of cancer cells amongst millions of normal cells. Sonification is the process of changing data into sound. This has been used in other areas of medicine like EKGs, but has not yet been used for pathologic cancer diagnosis. The aim of this project was to create a tool by sonifying the visual slide data so that normal and breast cancer tissue could be distinguished.

Methods: 15 digital slides of breast cancer were selected from the Cancer Genome Atlas data portal. Using Qupath, slides were divided into 100 µm2 square tiles. Optical density (OD), hematoxylin & eosin concentration, and saturation were measured and collected for selected areas in each slide. These were imported into TwoTone, a sonification program and soundtracks were created for each slide. Parameters in TwoTone were adjusted to create each prototype. The first prototype was played by piano. The second prototype had piano for OD sum, others as organ and harp. The third prototype had OD sum as violin, others as harp and piano. Overall, 3 prototypes were created for 15 digital slides. 12 participants were asked to listen to each soundtrack and indicate where they believed the transition between normal tissue and cancer tissue was.

Results: The survey was completed by 2 pathologists, 2 teenagers, and 6 non-medical adults. The third prototype was the most successful in identifying the transition from normal to cancerous tissue. The average amount of participants that got the correct answer for prototypes 1, 2, and 3, were 39%, 39%, and 87%, respectively. A logistic regression model was performed and showed that the odds of participants getting the correct answer was 4.8 times higher in prototype 3 than either of the other prototypes, significantly ($p<0.0001$).

Discussion: The goal of this project was to create a prototype that could effectively aid pathologists in diagnosing breast cancer. Through 3 prototypes, a final tool was created that was efficient, accurate, accessible, and appealing to listen to. This multisensory tool can be valuable to pathologists in detecting and diagnosing breast cancer.

Research theme 1: Cancer Biology
Research theme 2: Digital Pathology
Research theme 3:

Presenter's Name: Vo, Meggie

Additional Author(s): Peng T

Abstract Title: Mitochondrial ROS-induced SerpinA3 expression protects cardiomyocytes against Doxorubicin-induced injury

Abstract:
Introduction: Cancer and cardiovascular disease are the leading cause of death in Canada. Doxorubicin (DOX) is a widely used drug that induces cancer cell death through reactive oxygen species (ROS) production. However, its usage has been shown to worsen cardiac outcomes down the line in cancer patients. Thus, there is a need for biomarkers to predict cardiotoxicity and create preventative interventions for DOX-induced cardiac injury.

SerpinA3 is a target of clinical interest due to its overexpression in various cancers. Notably, its increased expression has been linked to poor prognosis of cancer and cardiovascular disease. However, it remains unknown if serpinA3 plays a role in DOX-induced cardiac injury. Our preliminary study showed DOX treatment increased serpinA3N (ortholog of serpinA3) expression in primary neonatal cardiomyocytes and mouse hearts. Pretreatment with recombinant serpinA3 protein reduced injury in DOX-induced cardiomyocytes, suggesting serpinA3 protects cardiomyocytes from DOX injury. Our study investigates serpinA3 expression in cardiomyocytes and its efficacy against DOX-induced cardiotoxicity.

Methods: AC16 human cardiomyocyte cell line was infected with recombinant adenoviruses expressing serpinA3 (Ad-serpinA3) or hemagglutinin (Ad-HA) as a control, then incubated with DOX (5 μM) or saline for 24 hrs. Lactate dehydrogenase (LDH) assay was performed to assess cytotoxicity. Cardiomyocytes were pretreated with mito-TEMPO (20 nM) or a vehicle, followed by DOX treatment to assess the role of mitochondrial ROS in serpinA3 expression. SerpinA3 gene and protein expression were measured via RT-qPCR and western blot analysis, respectively.

Results: Cardiomyocytes treated with DOX had increased gene and protein expression in serpinA3. Pretreatment with mito-TEMPO prevented mitochondrial ROS production and reduced serpinA3 gene expression in DOX-induced cardiomyocytes. Ad-serpinA3 infection increased protein levels of serpinA3 and decreased levels of LDH produced by cardiomyocytes after DOX treatment.

Discussion: These results suggest that serpinA3 plays a protective role in DOX-induced cardiotoxicity. It also suggests that mitochondrial ROS mediates DOX-induced serpinA3 expression in cardiomyocytes. Targeting serpinA3 as a potential biomarker to predict cardiac injury development in patients receiving chemotherapy may be a useful approach in determining cardiac preventative measures for those undergoing chemotherapy in clinical settings.

Research theme 1: Cardiovascular, Respiratory Health, and Metabolic Diseases
Research theme 2:
Research theme 3:

Presenter's Name: Liddy, Amanda

Additional Author(s): Hong M, Baines K, Stuivenberg G, Figueredo R, Al K, Burton JP, Maleki Vareki S

Abstract Title: Enhancing anti-tumor and gut microbial responses to anti-PD1 immunotherapy through Akkermansia muciniphila supplementation in pancreatic cancer

Abstract:
Introduction: Providing adjuvants for immunotherapy for advanced and metastatic pancreatic adenocarcinoma (PDAC) is necessary for improved patient survival. Supplementation with Akkermansia muciniphila (AM), a bacterium routinely found enriched in immunotherapy responders, has the potential to modulate the immune system and increase the efficacy of immunotherapy. This study investigates the effects of oral AM supplementation in combination with anti-PD1 immunotherapy, in modifying the gut and tumor microbiome and T-cell activation in PDAC.

Methods: Subcutaneous KPC tumor-bearing mice (n=24) were orally administered AM or PBS and intraperitoneally administered anti-PD1 or isotype control over the course of three weeks. At endpoint, tumor and spleen tissues were harvested for immune profiling by flow cytometry. To further investigate the effects of AM treatment on immunotherapy response, an inducible PDAC mouse model (n=21) was used, and pancreas tissues were harvested for immune profiling after similar treatment with AM+anti-PD1. Additionally, stool was collected at various timepoints throughout both experiments to be characterized by 16S rRNA gene sequencing using low abundance microbiota methodology. To elucidate the anti-tumor and immunomodulatory effects of AM in-vitro, proliferation, motility, epithelial-mesenchymal transition, and wound healing assays will be completed with KPC cells, and migration, activation, and effector capability assays will be completed with T-cells, using varying concentrations of AM cell free supernatant (CFS) in the growth media.

Results: In the tumors of AM+anti-PD1 treated KPC mice, there was a significant increase in the expression of T-cell activation markers, ICOS and PD1, on CD8+ T-cells. Systemically, there was less expression of ICOS and PD1 on CD8+ T-cells, suggesting that these cells may be migrating from the spleen to the tumors in response to treatment. There were significant increases in T-cell activation in the pancreas and spleen of PDAC mice treated with AM+anti-PD1, coupled with decreased T-cell exhaustion in the pancreas. Additionally, in-vitro KPC cell proliferation was significantly decreased at 15% and 20% CFS.

Discussion: This study will provide a better understanding of the role of adjunct bacterial-based therapy for combination treatment with immunotherapy in pancreatic cancer. Combining immunotherapy with an AM probiotic may enhance the anti-tumor immune response and directly affect tumor growth.

Research theme 1: Cancer Biology
Research theme 2:
Research theme 3:

Presenter's Name: Wang, Xuan

Additional Author(s): Khan A, Zhang Q

Abstract Title: Characterizing the Amygdala Involvement in Sudden Unexpected Death in Epilepsy: A Pathology and MRI Correlation Study

Abstract:
Introduction: Sudden unexpected death in epilepsy (SUDEP) remains a significant cause of mortality among epilepsy patients, yet its underlying mechanisms remain poorly understood despite ongoing research efforts. Previous studies have indicated alterations in the amygdala during seizures in epilepsy patients, suggesting their potential contribution to SUDEP. We hypothesize that physical alterations, such as changes in volume, within the amygdala might play a role in SUDEP. Given the intricate structure of the amygdala's subnuclei, which poses challenges for visualization in MRI scans, and the potential for distortion during histology slice preparation, an integrated approach is imperative.

Method: Twelve post-mortem amygdala sections from the right and left hemispheres, obtained from three SUDEP and three non-SUDEP cases, underwent 9.4T T2-weighted MRI scans at the Robert Research Institute. After that, histological slices stained with HE/LFB were prepared at the London Health Science Center. Annotations of histology slides were validated by a neuropathologist. Co-registration of MRI and histology slices was performed using the tensor image registration library to correct for deformations during preparation. Annotations were then transferred onto MR images for segmentation and volumetric analysis using 3D slicer software. Volume comparisons between SUDEP and non-SUDEP cases will be conducted.

Results: Two cases were analysed, including 16 histology slices and 480 MR images from the left and right amygdala. Preliminary analysis revealed deformations in histological slices, highlighting the necessity for co-registration with MRI. Further results are forthcoming.

Discussion: Traditional approaches to amygdala volume reconstruction have primarily utilized either MRI or histology independently, each with its limitations. Our integrated approach demonstrates enhanced visualization and segmentation, laying the groundwork for comparative analysis between SUDEP and non-SUDEP cases. These initial findings offer promising avenues for further investigation.

Research theme 1: Digital Pathology
Research theme 2: Pathobiology of Neurologic Diseases
Research theme 3:

Presenter's Name: Suthakaran, Karshana

Additional Author(s): Schmid S

Abstract Title: Examining the Impact of Environmental Enrichment on Autism Spectrum Disorder Through the Use of Cntnap2 Knockout Model Rats

Abstract:
Introduction: Autism Spectrum Disorder (ASD) is a prevalent neurodevelopmental disorder in Canada. One of the primary behavioural symptoms of ASD is an exaggerated startle response to sensory stimuli. While pioneering research has explored the benefits of environmental enrichment on neural plasticity and startle response in various neurodevelopmental disorders, there remains a significant gap in ASD research. Therefore, employing the Cntnap2 homozygous knockout rat model, which effectively mimics autism-like symptoms, this study aims to investigate the effects of environmental enrichment (EE) in laboratory settings. The study will assess how housing the rats in EE cages can change autism-related phenotypes, specifically startle responses, behaviour, exploration, and social interactions. It is hypothesized that the EE cages will modify acoustic startle response (ASR) and augment prepulse inhibition (PPI), simultaneously enhancing exploratory and social behaviours.

Methods: In order to test the hypothesis, knockout and wild-type rats were housed in EE cages from birth to the end of juvenile period and compared to rats raised in standard cages. Using a pressure-sensitive platform, the ASR and PPI were measured at the juvenile and adult stages to investigate auditory processing. Open field tests using open-top chambers and sociability tests were also performed to examine exploratory behaviours and social interactions, respectively. A One Health approach will be utilized to identify relevant stakeholders that are pertinent to this study.

Results: The results of the data analysis from the testing phase are anticipated to be available in March. It is expected that EE will lead to a decrease in startle reactivity and an increase in PPI. Moreover, EE rats are likely to exhibit elevated levels of exploratory behaviour and sociability. These outcomes are consistent with the improvements observed in studies examining the effects of EE in the context of schizophrenia and other autism rat models.

Discussion: The findings from this research and subsequent One Health integration will advance our understanding of the impact of EE on sensory processing within the ASD framework. It could facilitate translational research between Cntnap2 knockout rat models and humans with autism, focusing on the potential of EE to alleviate symptoms. Furthermore, it could inform effective interventions and influence public health policies and environmental management strategies.

Research theme 1: One Health
Research theme 2:
Research theme 3:

Presenter's Name: Sulman, Muhammad

Additional Author(s): Agbar SA, Sidahmed A

Abstract Title: Quantitative analysis of eplet load in heart transplant success: Evaluating the significance of mismatches across different HLA loci

Abstract:
Introduction: HLA antigen mismatches are known to be a contributor to the failure of transplanted hearts by increasing the likelihood of immune rejection. Polymorphic residues on the surface of HLA molecules, known as eplets, are the key elements recognized by the recipient's immune system, leading to transplant rejection. This study aims to find associations between the number of eplet mismatches at different loci, and time to the first incidences of rejection and failure.

Methods: To evaluate the effect of mismatches, over 100 donor-recipient pairs were HLA-typed at high resolution. Heart biopsies collected at regular intervals, were graded for acute cellular rejection by pathologists. A survival analysis was conducted, controlling for clinical factors (Age, BMI, etc.) to obtain significance of the associations between eplet mismatches and adverse outcomes including rejection and failure.

Results: Eplet mismatches in HLA-DQ significantly increase the incidence of Grade 2R (moderate) rejection. Increased participants may be required to better understand the role of eplet mismatches in adverse outcomes at other HLA loci.

Discussion: Eplet mismatches at HLA-DQ significantly increase the risk of moderate rejection. This highlights the potential of eplet matching to guide personalized immunosuppressant dosing and effective patient-recipient matching for heart transplantation.

Research theme 1: Bioinformatics and Data Science
Research theme 2: Regenerative and Transplantation Medicine
Research theme 3:

Presenter's Name: Liu, Eric

Additional Author(s): Lin A, Wang E, Ling C, Zhang Q

Abstract Title: A deep active learning framework for mitotic figure detection in Glioblastoma histology images

Abstract:
Introduction: Accurate identification of Mitotic Figures (MFs) plays a pivotal role in cancer diagnosis and grading. However, manual counting of MFs on histology images can be challenging and time-consuming. To overcome these challenges, we proposed an active learning framework with a tailored deep learning model to conduct preliminary screenings and annotations, to aid pathologists' daily practice.

Methods: 100 H&E stained whole slide images (WSIs) of glioblastoma were collected from the TCGA database. MFs on two WSIs were manually annotated and verified to serve as an initial dataset to train our customized YOLOv8 model. Data pre-processing and augmentation were performed on additional unlabeled WSIs before being processed by our model. A tri-class thresholding strategy was implemented to triage MFs with ambiguous morphology prior to pathologist review. To make the framework more accessible, this annotation and detection pipeline is integrated into a web-based platform (AI4Path).

Results: Out of the total of 100 glioblastoma WSIs, 18 were excluded due to low image quality or lack of MFs. With the aid of active learning, pathologists are only required to review MFs with uncertain morphology. This will significantly reduce the required human effort and accelerate the annotation process. As a result, eighty-two glioblastoma WSIs have been annotated by our deep learning model, and were reviewed by trained research assistant. Furthermore, 21 of these 82 glioblastoma WSIs have been verified by at least one pathologist. The final annotations include 804 normal MFs, 728 atypical MFs, and 1,955 granular MFs. Preliminary results also showcase our method's potential in balancing precision and recall, utilizing pathologist-verified samples for validation. Our method has achieved average scores of 82.48% for recall and 82.92% for precision.

Discussion: Accurate mitosis counting is crucial in cancer diagnosis. Our study leverages a deep learning method within an active learning framework to reduce manual effort in identifying MFs from glioblastoma WSIs, making the process more efficient and reliable. Moving forward, we aim to further refine this approach by providing more customizable settings, and enhancing its application across various other cancer types with the ultimate goal of improving diagnostic outcomes with fewer data and minimal manual counting.

Research theme 1: Digital Pathology
Research theme 2:
Research theme 3:

Presenter's Name: Holder, Natasha

Additional Author(s): Shimizu M, Cecchini M, Howlett C, McCord C

Abstract Title: Glandular Odontogenic Cyst: Molecular Analysis using Targeted Next-Generation Sequencing

Abstract:
Introduction: Glandular odontogenic cyst (GOC) is an uncommon developmental cyst of the jaws. GOC is unique to most cysts found in the jaws in that it can have variation in clinical presentation and may behave aggressively. Although benign, aggressive lesions can cause local bony destruction and have a high rate of recurrence, demonstrating some similarity to neoplastic lesions. The molecular pathogenesis of GOC has rarely been investigated and remains unclear. This study aims to use targeted next-generation sequencing techniques to identify potentially pathogenic nucleotide variations in GOC, which may help in understanding the biologic behaviour of these lesions. Due to the rare nature of these lesions, this study also aims to contribute histopathologic and clinical data of GOC found within our archives to the literature. We hypothesize that glandular odontogenic cyst shows distinct pathogenic nucleotide variations at both the DNA and RNA level.

Methods: All samples of GOC and odontogenic cysts with features of GOC from 2003-2022 were retrieved from the archives. Clinicopathologic data was gathered from the pathology reports and summarized. Histopathologic features were identified and frequency of known microscopic criteria were recorded and summarized. Targeted next-generation sequencing was performed to interrogate a panel of a 135 cancer driver genes and 49 fusion driver genes in GOC.

Results: A total of 99 specimens were identified from the archives. 51 of these were diagnosed as glandular odontogenic cyst. Within this GOC group, the mean age was 51.8 years old with a male predilection. Most were found in the posterior mandible (54.9%). Histopathologic features most identified in GOC were clear cells, variable thickness in the cyst epithelial lining, and eosinophilic cuboidal cells. Histologic diagnosis of GOC was variable amongst the group. Tier I/II variants in NRAS and TP53 genes were identified in one case of GOC. No pathogenic RNA fusions were found.

Discussion: Diagnosis of GOC is based on microscopic features of the lesion, with criteria based on the limited cases reported in the literature. In our samples, we found a frequency of histopathologic features that differs from those found in the literature. Contribution of this data could influence diagnostic decision making in the future. Our study is also the first to identify these genetic variants in GOC, which may provide insight into the molecular pathogenesis of these lesions.

Research theme 1: Oral Biology and Medicine
Research theme 2:
Research theme 3:

Presenter's Name: Yang, Jingwen

Additional Author(s): Yang JW, Peng TQ

Abstract Title: Determining the interaction between junctophilin-2 and junctin by the BiFC assay

Abstract:
Introduction: Junctophilin-2 (JP2) is an important structural protein in forming junctional membrane complexes, which are essential for the excitation-contraction coupling of cardiomyocytes. Junctin (JCN) is an accessory protein of the Sarco/endoplasmic reticulum Ca2+ release unit that interacts with RyR2 and Calsequestrin. Our recent study found a direct interaction between JP2 and JCN. This study investigated the JP2 binding domain in JCN.

Methods: The BiFC assay was used to determine the interaction between JP2 and JCN. Human JP2 gene was cloned into pBiFc-VC155 and human JCN gene was cloned into pBiFc-VN155. The resulting plasmids pBiFC-VC155/JP2 and pBiFC-VN155/JCN were co-transfected into A549 cells. Twenty-four hours later, the GFP signal was monitored under a fluorescence microscope. Western blot was performed to determine the expression of human JP2 and JCN in A549 cell lysates. A mutant of human JCN with 1-22 residues deleted was cloned into pBiFC-VN155. The resulting plasmid pBiFC-VN155/JCNfj1-22 was co-transfected with pBiFC-VC155/JP2 in A549 cells and fluorescent signal was monitored by fluorescence microscope.

Results: Fluorescence signal was observed in A549 cells after co-transfection with pBiFC-VC155/JP2 and pBiFC-VN155/JCN. As a control, co-transfection with pBiFC-VC155 and pBiFC-VN155 did not display any fluorescence signal in A549 cells. Future experiments will confirm the expression of human JP2 and JCN in A549 cells after co-transfection and co-immunoprecipitation assay will verify the interaction between JP2 and JCN. Future study will also determine the interaction between JP2 and JCNfj1-22 by the BiFC assay.

Discussion: We confirmed the interaction between JP2 and JCN by the BiFC assay. Future study will identify the JP2 binding domain in JCN using the same approaches.

Research theme 1: Cardiovascular, Respiratory Health, and Metabolic Diseases
Research theme 2:
Research theme 3:

Presenter's Name: Sreeram, Aparna

Additional Author(s): Khan ZA

Abstract Title: Association Between Enhanced Adipogenesis and Diabetic Neuropathy in Bone Marrow

Abstract:
Introduction: Diabetes mellitus is a prevalent disease that causes significant morbidity due to its induction of numerous secondary vascular complications. The bone marrow is a major target of diabetic complications, exhibiting osteopenia, neuropathy, and accelerated adipogenesis. Studies have identified a correlation between nerve fibre neuropathy and bone loss, and our laboratory has reported heightened adiposity in the bone marrow of diabetic rodent models. However, a comprehensive understanding of the relationship between neuropathy and adipogenesis remains unknown. Based on these findings, I hypothesize that decreased innervation of bone marrow is causally linked to elevated bone adiposity in diabetic mice compared to non-diabetic counterparts.

Methods: Previously, our laboratory induced type-1 diabetes in C57BL/6 mice and acquired histological samples of bone tissue. To test this hypothesis, Nissl staining with cresyl violet dye and immunofluorescence staining for the neuron-specific Rbfox3 protein was employed alongside DAPI counterstaining to visualize neuronal density and distribution within the tibia and femur bone tissue of diabetic and non-diabetic mice. PLIN-1 immunostaining will be used to identify adipocytes and assess their density and spatial arrangement in relation to neurons within bone tissue. Image analysis will be performed using QuPath.

Results: Cresyl violet staining was positive in the cytoplasm of all cells within bone and retina tissues, demonstrating a lack of specificity for neurons. However, immunofluorescence staining for Rbfox3 showed potential for specifically detecting neurons. The ganglion cell layer of mouse retinal tissues exhibited positive staining for Rbfox3 in nuclei and perinuclear cytoplasm. Contrastingly, photoreceptor cells were negative for Rbfox3, suggesting specificity for neurons. Rbfox3-positive cells were also found to be dispersed throughout the bone tissue of the femur and tibiae, exhibiting staining in nuclei and cytoplasm. I expect that Rbfox3-positive cells will be localized proximal to PLIN1-positive cells within the tibia and femur bone marrow, and that diabetic bone tissue will show diminished neuronal staining coupled with elevated PLIN1 staining in comparison to non-diabetic bone tissue.

Discussion: These results optimize methods for identifying post-mitotic neurons in bone marrow and offer insights into the mechanisms underlying diabetes-induced alterations in bone microarchitecture.

Research theme 1: Cardiovascular, Respiratory Health, and Metabolic Diseases
Research theme 2: Digital Pathology
Research theme 3: Test Utilization, Optimization and Quality Assurance

Presenter's Name: Volcko, Lauren

Additional Author(s): Frisbee S

Abstract Title: Facilitators and Barriers of Implementing Digital Interventions for Diabetes: A Scoping Review

Abstract:
Background: Diabetes mellitus, a significant global health challenge, affects millions worldwide and imposes substantial costs on healthcare systems. Despite advancements in treatment, many individuals fail to meet treatment targets, leading to secondary complications with associated additional costs. Although not widely implemented, the effectiveness of digital interventions to support diabetes self-management has been shown. This scoping review aims to investigate the utilization of these digital interventions in clinical settings and identify barriers and facilitators to their implementation.

Methods: This review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement for Scoping Reviews (PRISMA-ScR). Relevant articles published between January 2010, and November 2023 were identified through Scopus, EMBASE, PsychInfo, ProQuest, CINAHL and PubMed. Included studies were peer-reviewed, primary studies, describing type 1 and type 2 diabetic or pre-diabetic patients over 18 years old. Qualitative analysis will be used to identify themes surrounding barriers and facilitators for implementation based on the perceptions of both providers and patients in selected articles.

Results: In total, 1038 were screened and 22 articles were included in the final review. Extraction and synthesis of the results remain ongoing. Preliminary results indicate that barriers for providers include concerns of integration into clinical workflow, and a lack of organizational framework for implementation of digital interventions. Similarly, patient barriers centre around a lack of motivation and participation with "faceless" advice. Relevant findings from data extraction of the thematic analysis will also be included in the results.

Discussion: The results from this scoping review can provide a foundation for digital health implementation and identify priorities to achieve broader adoption addressing the challenge that diabetes poses globally. A One Health approach will be used to identify relevant key stakeholders to highlight the need for collaboration between disciplines to holistically address diabetes.

Research theme 1: One Health
Research theme 2:
Research theme 3:

Presenter's Name: Kawa, Daniel

Additional Author(s): Kiser P, Betts DH

Abstract Title: Characterizing p66Shc-Dependent Effects on Pluripotent Stem Cell Fate Using Teratomas for Comparative in vivo Multi-Lineage Differentiation Modeling

Abstract: When stem cell regulation is disrupted during early ontogenesis, resulting defects in developmental process timing and synchrony often elicit maturational delay and arrest. Among the key drivers of stem cell fate and state decisions are mitochondrial homeostasis, metabolism, and cellular redox state – linked to stem cell identity and fate through the p66Shc adaptor protein. Previously, our lab used CRISPR/Cas9 to induce p66Shc knockout (KO) in mouse embryonic stem cells (mESCs) that produced murine xenograft teratomas with skewed and immature development versus wildtype (WT). While their cellular diversity, regions of tissue-like complexity, and vascularized 3D environment make teratomas promising tools for modeling early development in vivo, their compositional and maturational heterogeneity have presented hurdles for elucidating p66Shc-dependent effects thereon through bulk gene expression analysis. Building on comprehensive computational frameworks for relevant teratoma single-cell RNA sequencing (scRNA-seq) analyses published in the literature, we propose employing this approach alongside spatial validation to surmount these challenges, and to distinguish between p66Shc KO-induced maturational arrest versus delay. Currently, we are optimizing a cell culture adaptation assay to acclimate WT and p66Shc KO mESCs to feeder-free conditions, which we have previously shown to abrogate their phenotypic differences to an equivalent ground pluripotency state by RT-qPCR. To generate teratomas, each NOD/SCID IL-2R -null mouse will receive a subcutaneous injection of either WT or p66Shc KO mESCs. The mice will be sacrificed and teratomas excised either collectively once the first reaches 1.5 cm in diameter ('same time' cohort), or individually upon reaching this size or a humane endpoint ('same size' cohort). Following gross tumour measurements, qualitative histological assessments of teratoma germ layer composition and tissue maturity will form the basis of, and serve as a tool to validate, comparative scRNA-seq cell-type characterization, teratoma heterogeneity, and cell-type maturity analyses. Collectively, we anticipate this research will provide an unprecedently robust evaluation of p66Shc KO-induced effects on cell fate decisions during early development. This will provide a platform towards the elucidation of new mechanisms that underpin the mitochondrial control of this fundamental process that goes awry in multiple human pathologies.

Research theme 1: Bioinformatics and Data Science
Research theme 2: Regenerative and Transplantation Medicine
Research theme 3:

Presenter's Name: Cheung, Tiffany

Additional Author(s): Gholami H, Maleki S

Abstract Title: Changes in Systemic Cytokine Levels from Gut Microbiota Modulation with Antibiotics and Immunotherapy

Abstract:
Introduction: Success of immune checkpoint inhibitors (ICIs) as a cancer therapy is limited by tumour immunogenicity and gut microbiota composition, whose roles are currently unclear in ICI response. Neuroblastomas are characterized by their low immunogenicity and poor response to ICIs. The Maleki lab has previously sensitized neuroblastomas to ICIs by inducing mismatch repair (MMR) deficiency, rendering the tumour immunogenic as evidenced by reduced tumour volumes in induced-deficient MMR (idMMR) neuroblastoma-bearing mice after anti-CTLA-4 treatment. However, the effects of antibiotics on gut microbiota modulation on immunotherapy response have not been investigated in an idMMR neuroblastoma model regarding their influence on systemic cytokine levels during gut bacteria modulation and immunotherapy. IL-2 shows potential as a combination therapeutic with ICIs, and elevated IL-6 levels are linked to ICI-related toxicities. Therefore, I hypothesize that systemic IL-2 and IL-6 levels in idMMR neuroblastoma-bearing mice given antibiotic treatment can be used as predictive markers for anti-CTLA-4 response.

Method: Mice will be given an antibiotic cocktail consisting of 1mg/mL ampicillin, 1mg/mL neomycin, 0.5mg/mL vancomycin, and 1mg/mL metronidazole to deplete their gut microbiota. Mice will be subcutaneously injected with idMMR neuroblastoma cells and administered 3 doses of anti-CTLA-4 once tumours are palpable. Serum will be collected between antibiotic administration, tumour injection, anti-CTLA-4 treatment, and at the endpoint for cytokine analysis. IL-2 and IL-6 will be quantified using enzyme-linked immunosorbent assays (ELISA) from collected serum to compare changes in cytokine levels between treatments.

Results: Decreased levels of IL-2 and increased levels of IL-6 are expected following antibiotic treatment and tumour injection, whereas increased levels of IL-2 and decreased levels of IL-6 are expected following anti-CTLA-4 treatment.

Discussion: This project will enhance our understanding of changes in cytokine levels in response to antibiotics and immunotherapy, providing insight into the factors influencing immunotherapy response that are currently hindering strategies to improve ICI success in intractable cold tumours. Investigating IL-2 and IL-6 further elucidates their roles in influencing immune responses in antibiotic treatment and immunotherapy, contributing to our understanding of the complex dynamics involved in cancer immunotherapy.

Research theme 1: Cancer Biology
Research theme 2:
Research theme 3:

Presenter's Name: Feng, Kevin

Additional Author(s): Hallett M, Bjazevic J

Abstract Title: Predictive Modeling of Kidney Stone Composition Using Machine Learning and Clinical Data

Abstract:
Introduction: Kidney stones are a common urological condition that occurs when mineral and organic deposits form solid formations within the renal system. About one in ten individuals is affected by this condition, and it often causes severe pain when the stones pass through the urinary tract. Understanding the composition of kidney stones is essential for developing effective treatment and prevention methods, given the variety of stone types and corresponding treatment options available. Currently, clinicians can only determine the composition of kidney stones after removing them from patients. Therefore, we aim to use machine learning methods to build predictive models to analyze clinical data and identify kidney stone composition without invasive procedures.

Methods: A group of 661 individuals with kidney stones were studied to collect data on stone composition, 24-hour urine profiles, serum biochemistry, and patient demographic and medical history. Using this clinical data, we trained a binary classification random forest machine learning model to determine if patients would have stones containing calcium monohydrate, calcium dihydrate, calcium phosphate, apatite/brushite, uric acid, struvite, and cysteine. The sensitivity, specificity and F1 score were used to evaluate the model's performance.

Results: Using the F1 score to evaluate the performance of the classification model using a threshold of greater than 0.75 as a good model, the binary classification random forest machine learning model was able to determine whether a stone would contain calcium monohydrate or calcium dihydrate. Both calcium monohydrate and calcium dihydrate models could determine true positive cases with a sensitivity of 0.933 and 0.808, respectively. However, they cannot determine true negative models with specificity values of 0.136 and 0.4, respectively. The binary classification random forest machine learning could not determine whether kidney stones contain calcium phosphate, apatite/brushite, uric acid, struvite, and cysteine.

Discussion: Preliminary findings indicate that a basic binary classification random forest model struggles to accurately predict the composition of kidney stones. However, as this model serves as a benchmark for comparison, more advanced deep learning techniques will be explored in the project's progression to address the limitations observed in the random forest model.

Research theme 1: Bioinformatics and Data Science
Research theme 2:
Research theme 3:

Presenter's Name: Faulkner, Ashley

Additional Author(s): Cecchini M, Tran C

Abstract Title: Assessing the concordance of gross and microscopic margins in pancreatic cancer resections: a retrospective cohort study from January 2013 to December 2022

Abstract:
Introduction: Pancreatic cancer is one of the leading causes of cancer death, with surgical resection serving as the only curative treatment option. Gross and microscopic evaluation of pancreatic cancer specimens is critical to determine prognostic and treatment options. One component includes evaluation of surgical margins, which can prove challenging due to specimen complexity and high rate of neoadjuvant treatment. There is limited understanding of the accuracy of gross margin assessment, and the concordance rates between gross and microscopic measurements. In this study, we evaluated the concordance between gross and microscopic margin assessment in pancreatic cancer resections and identified key factors affecting their concordance or discordance.

Methods: A retrospective cohort study was performed at London Health Sciences Centre, London, Ontario, Canada. We evaluated all pathologically staged pancreatic cancers over a 10-year period (January 2012-December 2022). For each case, we used the pathology report to collect data regarding resection type, grossing personnel, microscopic tumour site, histologic type, grade, and treatment status. The concordance of gross and microscopic margins was determined by comparing the gross and microscopic measurements. A univariate analyses will be performed to compare both groups (concordant and discordant) as well as a multiple regression analysis to identify which outstanding factors affect margin concordance.

Results: A total of 318 cases were included in the study, including 253 pancreaticoduodenectomy (PDE) and 57 distal pancreatectomy (DP) specimens. The gross and microscopic margin status was concordant in 17% of the specimens (22% for PDE resections, and 15% for DP specimens). The most common histologic subtype was adenocarcinoma (85%), and the pancreatic head was the most common tumour site (71%). Of those with concordant margins, only 35% had both margin location and R status correlation.

Discussion: Among pancreatic resection specimens, there is high discordance between gross and microscopic margin assessment. Given this, submission of all margins is important for definitive microscopic evaluation and prognostic determination. Future statistical analyses will identify the factors that have a significant effect on this discordance.

Research theme 1: Bioinformatics and Data Science
Research theme 2: Cancer Biology
Research theme 3: Test Utilization, Optimization and Quality Assurance

Presenter's Name: Coats, Jennifer

Additional Author(s): Lin S, Romagnoli T, Cecchini M

Abstract Title: Analysis of tumor cellularity variance in simulated core needle biopsy specimens across resected lung cancer cases.

Abstract:
Introduction: Core needle biopsies (CNBs) are routinely used for the diagnosis of lung cancer, and a subset of these biopsies are insufficient for diagnosis or ancillary testing. Optimizing tumor cellularity is critical to ensure there is sufficient material for histological analysis and molecular testing. This study aims to elucidate the variability of tumor cellularity within resected specimens and examine the concordance of cellularity between corresponding resection and CNB specimens.

Methods: From The Cancer Genome Atlas, we obtained 180 digital slides, including 100 lung adenocarcinoma and 80 lung squamous cell carcinoma datasets. Additionally, 21 corresponding resection and CNB squamous cell carcinoma (SCC) histopathology slides from London Health Sciences Centre were obtained and digitized. Using QuPath, we annotated the slides, performed a total cell detection, and distinguished cancerous from non-cancerous cells. Following this, representative CNBs, measuring 0.25 mm x 2.5 mm, were simulated and tiled across the entire slide, and the number of tumor cells and cellularity were recorded within each simulated core.

Results: The study revealed varying tumor cell densities across different tumor regions, with adenocarcinoma cases showing the highest densities in the intermediate region and SCC cases in the central region. The proportion of biopsy cores in each resected tumor that were adequate for molecular testing was highest in the intermediate region of the tumor for both the adenocarcinoma and SCC cases. Furthermore, a robust correlation between the cellularity in CNB and resection specimens was identified, and significantly strengthened when cores devoid of tumor cells were excluded ($p < 0.01$, $R = 0.90$).

Discussion: We observed a spectrum of findings, with each tumor region having the highest average number of tumor cells and percent cellularity for a proportion of the slides. Similarly, we found that there is a spectrum of cellular variability between resected specimens and core biopsies, that is minimized by eliminating cores without viable tumor. These insights underscore the imperative for future research to integrate these findings with imaging data, aiming to refine algorithms for CNB targeting, thereby optimizing biopsy accuracy and diagnostic yield in lung cancer.

Research theme 1: Digital Pathology
Research theme 2:
Research theme 3:

Presenter's Name: Donovan, Justin

Additional Author(s): Ghafoor A, Deng I, Potter M, Gibson R, Joseph D, Pardy J, Adebiyi A, Siemon M, DeGroot CT, Arts E, Quiñones-Mateu M

Abstract Title: Enhanced detection of SARS-CoV-2 variants through wastewater surveillance: Insights for public health preparedness

Abstract: In the ongoing battle against COVID-19, early detection of emerging variants of SARS-CoV-2 has become paramount for effective public health interventions. Traditional clinical testing, while valuable, has shown limitations in providing comprehensive insights into the actual viral load and proportions of variant diversity within communities. Wastewater surveillance has emerged as a promising approach to fill this gap, offering a more insightful perspective on viral dynamics at the population level. Our study presents the results of a retrospective analysis of wastewater samples collected from London, ON, spanning from June 2021 to January 2023. Through deep sequencing analysis, we aimed to illuminate the temporal dynamics and genetic diversity of SARS-CoV-2 variants within the region. Our findings reveal a significant observation: low frequencies of variants such as BA.1, BA.4, BA.5 and BE.1 were detected in wastewater samples over two months prior to their first reported clinical arrival in Canada. This discovery underscores the critical significance of wastewater surveillance as an early flagging system for the arrival of novel variants. By identifying emerging threats before they manifest clinically, wastewater analysis provides a crucial window of opportunity for proactive public health responses. Leveraging this technology not only allows for the timely implementation of targeted interventions but also facilitates the allocation of resources to areas at higher risk of outbreaks. These findings advocate for the implementation and expansion of wastewater-based surveillance systems as integral components of future outbreak preparedness strategies. By incorporating wastewater surveillance into routine public health monitoring, we can enhance our ability to detect, track, and respond to emerging variants, ultimately mitigating the impact of infectious disease outbreaks on communities worldwide.

Research theme 1: Bioinformatics and Data Science
Research theme 2: Infection, Immunity, and Inflammation
Research theme 3:

Presenter's Name: Leung, Ginnian

Additional Author(s): Larsen F, Derouet MF, Zhang L, Asfaha S

Abstract Title: The effects of EZH2 inhibition on colitis-associated colorectal cancer initiation

Abstract:
Introduction: Colorectal cancer (CRC) is the second leading cause of cancer death in Canada. Inflammatory bowel disease (IBD) is a major risk factor, leading to colitis-associated colorectal cancer (CAC). We recently generated a CAC model in which tumors arise from DCLK1+ cells upon loss of adenomatous polyposis coli (APC), a tumor suppressor gene, and the induction of colitis. Interestingly, IBD patients display changes in histone modifications and the histone methyltransferase enhancer of zeste homolog 2 (EZH2), which generates repressive H3K27me3 marks. Furthermore, it has recently been proposed that EZH2 inhibition leads to the expression of endogenous retroviruses (ERVs), triggering a viral mimicry response (VMR) that reduces tumor growth. It is unknown how EZH2 inhibition affects CAC tumor initiation. We hypothesize that EZH2 inhibition decreases CAC by activating a VMR.

Methods: EZH2 inhibition can be achieved pharmacologically or genetically. For the pharmacological approach, Dclk1CreERT2;Apcf/f mice are treated with three doses of tamoxifen followed by five days of 2% dextran sodium sulfate (DSS) to induce colitis. Mice are given five doses of vehicle or 10 mg/kg GSK343, an EZH2 inhibitor. Colonic tumor number is assessed 14 weeks later. In a separate experiment, WT mice are treated with 10 mg/kg azoxymethane (AOM), 2% DSS, and five doses of vehicle or GSK343. Tumor number is assessed 20 weeks later. For the genetic approach, Ezh2ΔSET/ΔSET mice are crossed to our Dclk1CreERT2;Apcf/f mice. Dclk1CreERT2;Apcf/f;Ezh2ΔSET/ΔSET and Dclk1CreERT2;Apcf/f mice are treated with three doses of tamoxifen and DSS. Tumor number is assessed 14 weeks later. To investigate whether EZH2 inhibition activates a VMR, tissues from AOM/DSS mice treated with vehicle or GSK343 and tumors from Dclk1CreERT2;Apcf/f and Dclk1CreERT2;Apcf/f;Ezh2ΔSET/ΔSET mice will be analyzed by western blot for H3K27me3 and RT-qPCR for expression of ERVs and IFN response genes.

Expected Results: We expect reduced tumor number in AOM/DSS and Dclk1CreERT2;Apcf/f mice treated with GSK343 and Dclk1CreERT2;Apcf/f;Ezh2ΔSET/ΔSET mice compared to controls. Furthermore, we expect elevated expression of ERVs and IFN response genes and decreased H3K27me3 levels in AOM/DSS mice treated with GSK343 and Dclk1CreERT2;Apcf/f;Ezh2ΔSET/ΔSET mice.

Significance: This project will determine the role of EZH2 in CAC. Investigating the effects of EZH2 on CAC may uncover a novel therapeutic target for CAC.

Research theme 1: Cancer Biology
Research theme 2: Epigenetics
Research theme 3:

Presenter's Name: Monaghan Chow, Isabella

Additional Author(s): Greasley A, Zheng X

Abstract Title: Identification and Characterization of circCRIM1 expression profile in Cardiomyocytes

Abstract:
Cardiovascular disease (CVD) is the leading cause of death globally and affects approximately 2.4 million Canadians. Circular RNA, a group of covalently closed single stranded RNAs, have been found to be implicated in a variety of cardiac pathologies such as ischemia reperfusion injury and coronary artery disease. Circular CRIM1 (circCRIM1) has been shown to increase its expression following ischemia reperfusion injury (IRI), however its exact role in CVD has yet to be discovered and it has multiple isoforms reported. Based on our preliminary data that a novel circCRIM1 isoform consisting of exons 2-4 and 13 is up-regulated in IR injured heart cells in vitro, I hypothesize that this novel circCRIM1 isoform is expressed predominantly in cardiomyocytes. Here I will characterize circCRIM1 in human and mouse cardiomyocytes. I will also determine the expression of both isoforms across a variety of mouse tissues and observe expression levels in response to cardiomyocyte injury. Junction specific primers will be used to amplify circCRIM1 isoforms in HL-1 and AC16 cell lines. The stability and half-life of circCRIM1 will be determined by treating cells with RNaseR and actinomycin D. Mouse tissue will then be isolated and harvested to examine the expression of isoforms across tissues. In addition, I will detect circCRIM1 expression in cell lines with cellular injury induced by IRI, H2O2 and CoCl2. We expect to determine the expression profiles of circCRIM1 in cardiac tissue and observe changes of circCRIM1 expression following cellular injury. Discovering a potential gene regulator- circCRIM1-in the pathogenesis of cardiac diseases will expand the knowledge of the role circular RNAs have in IRI. A better understanding of this process will be helpful in the future development of effective biomarkers for diagnosis or treatment of CVD.

Research theme 1: Cardiovascular, Respiratory Health, and Metabolic Diseases
Research theme 2:
Research theme 3:

Presenter's Name: McConkey, Haley

Additional Author(s): Bouhamdani N, Leblanc A, Ben Amor M, Sadikovic B

Abstract Title: Diagnostic utility of DNA methylation episignature analysis for early diagnosis of KMT2B-related disorder: case report form national EpiSign-CAN trial

Abstract:
Introduction: While individually rare, rare diseases collectively impact an estimated 500 million people worldwide with an estimated 80% due to genetic causes. Advances in diagnostic technologies have improved our ability to read the genome, however, our ability to interpret these findings lags behind, resulting in an estimated 50 to 60% of patients remaining undiagnosed after extensive genetic testing. Assessing the epigenome, specifically DNA methylation profiles (also known as episignatures), has demonstrated utility as a diagnostic tool. EpiSign is the first clinical test for epigenomic analysis and the first national trial ("EpiSign-CAN") aiming to assess its utility as a screening or reflex test is underway.

Methods: The EpiSign test uses whole-genome methylation analysis to compare detected methylation changes in a patient to known episignatures associated to more than 125 rare disorders. EpiSign-CAN aims to obtain real-world evidence of utility in Canadian Genetics Clinics.

Results: A 4-year old patient seen in a New Brunswick Genetics Clinic was referred to EpiSign-CAN as a screening patient after their chromosomal microarray results were negative. Patient presented with speech delay, microcephaly, and dysmorphic features after an uncomplicated pregnancy and induced delivery at 39 weeks due to unexplained intrauterine growth restriction. Surprisingly, episignature assessment demonstrated concordance with the Dystonia 28, childhood onset (DYT28), which results from mutations in lysine methyltransferase KMT2B. Subsequent single gene sequencing confirmed a de novo heterozygous pathogenic variant in KMT2B: c.12_24dup (p.Ser9Glyfs*111).

Discussion: This case demonstrated an episignature for a disorder that was not considered in the differential diagnosis due to the defining phenotype, dystonia, being absent in the patient's clinical presentation. DYT28 median age of dystonia onset is 7-years. Our patient displayed no motor abnormalities; however, it is possible dystonia may appear as they age as more than 80% of patients with KMT2B mutations develop dystonia. This patient will now be followed closely for dystonia onset and will receive early access to a promising therapy called deep brain stimulation. In our case, EpiSign was particularly useful in providing an earlier diagnosis in a patient who would have received a large gene panel that did not include the causative gene (KMT2B) and would have then needed to wait for expanded clinical testing.

Research theme 1: Epigenetics
Research theme 2:
Research theme 3:

Presenter's Name: Jose, Pious

Additional Author(s): Olea-Popelka F, Castellani C, Cameron L

Abstract Title: Exploring Epigenetic Age Acceleration and Mitochondrial Dysfunction in Asthma

Abstract:
Introduction: Asthma is a respiratory condition with a substantial global health burden. asthma development involves predisposing genetics and environmental exposures such as animal allergens from pets, cigarette smoke, and air pollution. Therefore, a One Health approach considering environmental, animal, and human health is vital to understanding asthma. Although asthma mediated by type 2 (T2) inflammation is well understood, less is known about the often more severe non-T2 asthma. The field of epigenetics and mitochondriomics are tied to the values of One Health since they explore how our bodies adapt to these environmental effects. Thus, studying environmental effects through epigenetic regulation of gene expression, mitochondrial DNA (mtDNA), and epigenetic aging is vital to finding the pathogenesis of non-T2 asthma.

Methods: We examined the relationships between epigenetic age and mitochondrial (mt) dysfunction in asthma. Epigenetic age was calculated using Horvath, Hannum, SkinHorvath, PhenoAge, GrimAge and DunedinPACE clocks on publicly available datasets of two independent Asthma studies looking at bronchial (N=130) and upper airway epithelial (N=104) cells of 234 individuals. We also assessed the CpG sites related to mt hub genes associated with non-T2 asthma to find potential epigenetic markers for this subtype. We also plan to measure mt function and mtDNA copy number of immune cells involved in non-T2 asthma to assess whether mt dysfunction affects asthma severity.

Results: Preliminary data show that asthmatics have a greater epigenetic age acceleration (EAA) than non-asthmatics. In asthmatic patients, the SkinHorvath clock had an EAA of 3.60 years (p = 1.71e-3). The Horvath clock showed an EAA of 2.51 years (p = 7.00e-3). Hannum showed an EAA of 2.01 years (p = 3.50e-2). PhenoAge showed an EAA of 2.76 years (p = 4.14e-3). GrimAge showed an EAA of 1.08 years (p= 2.85e-2). DunedinPACE did not show a significant difference between patients and controls (p=9.10e-2). All clocks show a positive direction of effect. Expected results for future work include the identification of potential epigenetic markers for Asthma susceptibility and observations of mt dysfunction in immune cells associated with non-T2 asthma.

Discussion: Exploring connections between epigenetic age, mt dysfunction, and asthma subtypes through a One Health lens will increase our understanding of the development of asthma and uncover new therapeutic approaches.

Research theme 1: Bioinformatics and Data Science
Research theme 2: Epigenetics
Research theme 3: One Health

Presenter's Name: Charrette, David

Additional Author(s): Dong C, Darling M

Abstract Title: Expression of S100A7 in Soft Palate Dysplasia and Maxillectomy Margins.

Abstract:
Introduction: Oral squamous cell carcinoma (OSCC) is the 6th most prevalent malignancy. OSCC is preceded by or associated with potentially malignant lesions that have the potential to transform into cancer termed oral potentially malignant disorders (OPMDs). Currently, no single or set of biomarkers can reliably predict the malignant transformation rates of OPMDs to OSCC. S100A7 (Psoriasin) is a small calcium-binding protein which is upregulated in abnormally differentiating keratinocytes. S100A7 overexpression has been demonstrated in a variety of tissue types including epithelium of lung, ovarian, cervical, pancreatic, stomach, larynx, esophageal, skin, ER-positive breast, and oral dysplastic lesions and malignancy. S100A7 has been proposed marker for invasion as have several proteins involved in cell cycle regulation including Beta catenin, Ki-67, E-cadherin, BRAF, Geminin, and Mcm-2. Maxillectomy is a surgical procedure used to treat OSCC of the midface. It involves resection of tumors involving the orbit, nasal cavity, palate, paranasal sinuses, and alveolar bone. Resection requires margin of healthy tissue to minimize the risk of recurrence. Maxillectomy is usually combined with radiation and/or chemotherapy and has a poor prognosis with a 5-year survival of 40%. The hypothesis of this study is that S100A7 expression is increased in dysplastic lesions of the soft palate and in maxillectomy margins in cases of recurrence. The proposed mechanism is through association with proteins Mcm-2, Geminin, Ki-67, E-cadherin, BRAF and Beta-catenin.

Methods: This is a retrospective case-control study utilizing the Western University Oral Pathology and LHSC Hospital databases. Cases will be selected based on histopathological diagnoses and allocated to the following groups: dysplasia of the soft palate, maxillectomy margins, and normal tissue controls. All samples will be cut and stained using a standardized protocol for the following proteins: S100A7, Mcm-2, Geminin, Beta-catenin, E-cadherin, Ki-67 and BRAF. Specimen stained with S100A7 will be sent for Straticyte risk assessment. All specimens will be analyzed using QuPath software and undergo statistical analyses.

Results: In progress.

Discussion: The findings of this study could characterize a profile of biomarkers that would add objectivity and accurate prediction of transformation in OPMDs and recurrence of malignancy at clinically normal margins of OSCC resections.

Research theme 1: Cancer Biology
Research theme 2: Oral Biology and Medicine
Research theme 3:

Presenter's Name: Roes, Michael

Additional Author(s): Dick F

Abstract Title: A genome-wide CRISPR screen reveals TBX18 loss as a novel driver of enzalutamide resistance in prostate cancer

Abstract:
Prostate cancer (PC) cells can acquire resistance to the androgen receptor (AR) inhibitor enzalutamide (EZ). These cells can switch lineages from an adenocarcinoma to a neuroendocrine (NE) cell type that proliferate independently of the AR signaling pathway. Cancer genomic and molecular studies have noted heterogeneity among patients and identified genetic alterations that can promote the acquisition of EZ resistance and NE features in subsets of patients. However, there has yet to be a systematic analysis to characterize all molecular drivers of EZ resistance that can ultimately guide treatment development for patients. In this study, we hypothesize that a genome-wide, genetic perturbation study will identify novel molecular drivers of EZ resistance in PC. To categorize gene loss events in EZ-treated LNCaP PC cells, a genome-wide CRISPR knockout (KO) screen was performed. Pools of KO cells were treated with EZ or DMSO and analyzed by next generation sequencing to identify gene KOs that confer resistance to EZ. Gene ontology analysis of enriched genes following EZ treatment yielded a few unrelated functional terms. However, we found that several of these genes share protein structural domains, such as the TBX family of genes. We identified the transcription factor TBX18, important for urogenital development, as a putative EZ-resistance gene. We individually knocked out TBX18 using CRISPR-Cas9 in LNCaP cells. When seeded at low density and subsequently treated with EZ for 4 weeks, TBX18 KO cells formed significantly more colonies compared with control cells. However, when KO and control cells were treated with various concentrations of EZ for 6 days, we identified no difference in IC50 values. This suggests that TBX18 KO increases the propensity to acquire resistance over time. TBX18 KO cells also show increased mRNA expression of stemness and NE markers such as SOX9, ASCL1 and PEG10, suggesting that TBX18 KO promotes EZ-resistance through activation of stemness and NE expression programs. Finally, bioinformatic analyses of clinical PC patients showed that TBX18 deletion is found in 5% of cases and is associated with poorer overall survival. Overall, our results indicate that a genome-wide CRISPR screen can identify novel drivers of EZ resistance in PC cells. We identified that loss of TBX18 promotes EZ resistance, potentially through activation of NE expression programs, and may serve as a therapeutic target in a subset of EZ-resistant PC patients.

Research theme 1: Cancer Biology
Research theme 2:
Research theme 3:

Presenter's Name: Whittier, Abigail

Additional Author(s): Rutledge A, Knauer M, Stevic I

Abstract Title: Validation of the Roche Epstein-Barr virus serology assays

Abstract:
Background: Epstein-Barr virus (EBV) is associated with several diseases, including infectious mononucleosis and Hodgkin lymphoma. EBV serology testing can be used to characterize infection status and to assess the risk of EBV-associated diseases. At London Health Sciences Centre, EBV viral capsid antigen (VCA) IgG and IgM antibodies are tested on a Diasorin Liaison XL analyzer in-house, and serum samples for anti-EBV nuclear antigen (EBNA) IgG antibody testing are sent out to the Public Health Ontario Laboratory (PHOL). The aim of this study was to evaluate the performance (precision and method comparison) of EBV VCA IgG and IgM and EBNA IgG assays on the Roche e801 analyzer to consolidate and standardize these assays with a large panel of other infectious disease serology tests.

Methods: Precision was assessed using negative and positive quality control (QC) materials in the 5x5 manner. Instrument comparison involved analyzing both leftover patient serum samples which had been tested on the Diasorin Liaison XL, and anonymized PHOL serum samples tested on Bio-Rad Bioplex 2200, on the Roche e801. The Roche e801 was then compared qualitatively against the comparator methods for equivalency using predefined acceptable performance criteria.

Results: For precision, the negative and positive QC for EBV VCA IgG and IgM, and EBNA IgG Roche assays had total coefficients of variation of 2.8% and 3.6%, 1.6% and 1.5%, and 1.7% and 3.2%, respectively. The EBV IgM comparison had overall, positive, and negative agreements of 77.9%, 55.9%, and 100.0%, respectively and a Cohen's kappa coefficient of 55.9%, n=68. The EBV VCA IgG comparison between the Roche assay and the Diasorin Liaison XL assay had overall, positive, and negative agreements of 89.7%, 100.0%, and 75.6% respectively, and a Cohen's kappa coefficient of 78.2%, n=97. The Roche EBV VCA IgG assay was also compared to the Bioplex 2200 assay and had overall, positive, and negative agreements of 91.3%, 82.5%, and 100.0%, respectively and a Cohen's kappa coefficient of 82.5% n=80. The EBNA IgG comparison between the Roche assay and the Bioplex 2200 assay had overall, positive, and negative agreements of 97.5%, 95.0%, 100.0%, respectively and a Cohen's kappa coefficient of 95.0%, n=80.

Conclusion: The precision and method comparison results for all three Roche assays were clinically acceptable. Variation in data observed, particularly for IgM assays, may be due to variation in assay formulation.

Research theme 1: Test Utilization, Optimization and Quality Assurance
Research theme 2:
Research theme 3:

Presenter's Name: Burley, Leina

Additional Author(s): Al Jawhri MW, Yu M, French A, Cameron L

Abstract Title: Investigation of Metabolic Pathway Use by Th2 vs Th2-Th17 Cells

Abstract:
Introduction: Asthma is a chronic inflammatory disease of the airways that is typically considered to be mediated by either Th2 or Th17 cells. Recently, asthma severity was found to be associated with a dual-positive population of Th2-Th17 cells, indicating that a mixed inflammatory profile plays a role in severe asthma. Th2 cells are known to utilize glycolysis, fatty acid synthesis (FAS) and fatty acid oxidation (FAO) through the mitochondria. Th17 cells utilize glycolysis and glutaminolysis but downregulate FAO, leading to lipid accumulation. We examined whether Th2-Th17 cell metabolism aligns more with Th2 or Th17 cells and how this relates to pathogenicity. We hypothesized that Th2 cells differentiating to Th2-Th17 undergo metabolic rewiring involving the attenuation of FAO and mitochondrial function. As this would lead to fatty acid accumulation, we modeled this condition by treating cells with saturated fatty acids (SFA) and assessed if this influenced pathogenicity by increasing or decreasing IL-10 and/or increasing IL-17 production.

Methods: Th2 cells (IL2) and Th2-Th17 cells (IL2/TGFb/IL-21) were examined for differences in glycolysis (GLUT1), oxidative phosphorylation (CYCS), glutaminolysis (GLS, GLUD1), fatty acid synthesis (ACACA, FASN, FADS1) and fatty acid oxidation (SLC22A5) using qRT-PCR. How IL1b treatment of Th2-Th17 cells influenced metabolism and pathogenicity was also examined. Th2-Th17 cells will also be cultured with media enriched with saturated fatty acid (SFA) and compared to a control media enriched with polyunsaturated fatty acid (PUFA) to analyse if this influences pathogenicity by increasing IL-17 production.

Results: Our results demonstrate that Th2-Th17 cells showed an increase in GLUT1 and a decrease in CYCS, compared to Th2 cells, while no statistically significant differences were observed between Th2 and Th2-Th17 cells for genes associated with glutaminolysis, FAS or FAO. IL-1b treatment may reduce IL-10, more experiments are being performed. The results for the impact of SFA versus PUFA treatment on Th2-Th17 cell IL-17 production is forthcoming.

Discussion: Th2-Th17 cells may be upregulating glycolysis and have lower mitochondrial function, suggesting metabolic rewiring plays a role in increased IL-17 production and pathogenicity. These results highlight the potential for metabolism as a therapeutic target for severe asthma.

Research theme 1: Cardiovascular, Respiratory Health, and Metabolic Diseases
Research theme 2: Infection, Immunity, and Inflammation
Research theme 3:

Presenter's Name: Mui, Louise

Additional Author(s): Kerkhof J., McLachlin CM, McGee J, Sadikovic B, Goebel EA

Abstract Title: Examining the Concordance of Hereditary Cancer Gene Mutations between Normal Tissue, Tumor, and Germline Testing in Patients with High Grade Serous Ovarian Carcinoma

Abstract: BRCA1/2 germline testing and genetic counselling are standard of care for patients with high grade serous ovarian carcinoma (HGSOC). The introduction of tumor testing has proved to be a feasible and reliable method of detecting pathogenic variants in hereditary cancer genes. This can be performed reflexively at the time of surgical resection and could be used as a strategy to improve patient triaging for germline testing and clinical genetics referral; however tumor testing cannot readily distinguish somatic from germline mutations. As such, concurrent testing of non-tumor tissue at the time of surgical resection may further inform and refine the triage process. The objective of this study was to assess the concordance of hereditary cancer gene mutation detection between normal tissue, tumor, and blood in order to determine if germline pathogenic variants can be reliably detected using archived normal tissue.
Patients with HGSOC who had a pathologic variant identified by NGS tumor testing and received germline testing using a custom hereditary cancer gene panel (HCP) between April 2019 and November 2020 were identified. HCP testing was subsequently performed on formalin-fixed, paraffin-embedded archived normal tissue from the patients' original surgical resection. Results were compared between normal tissue, tumor, and germline (blood) testing and the concordance, false-negative, and false-positive rates were determined.

41 patients with HGSOC and a confirmed pathogenic variant in BRCA1/2 or other HCP gene on tumor testing were identified. Of these, 24 had the identical pathogenic variant identified by germline testing. HCP testing was then performed on archived normal tissue from 23 of the 24 patients. All germline variants were detected in normal tissue, demonstrating 100% concordance. Similarly, of the remaining 17 patients in which no pathogenic germline variant was identified, all matched normal tissue samples were negative for an HCP mutation, reflecting a 100% concordance rate between normal tissue testing and germline testing. No false positive or false negative results were identified.

These data provide support for the feasibility of NGS testing of normal tissue at the time of surgical resection to reliably identify germline pathogenic cancer gene variants in patients with HGSOC. Further, results from concurrent reflex testing of normal and tumor tissue may improve testing turnaround times and refine clinical genetics referral practices.

Research theme 1: Bioinformatics and Data Science
Research theme 2: Cancer Biology
Research theme 3: Test Utilization, Optimization and Quality Assurance

Presenter's Name: Shaker, Nader

Additional Author(s): Jackson-Boeters L, Darling M

Abstract Title: S100A7 expression in oral potentially malignant disorders: verrucous hyperplasia and verrucous carcinoma

Abstract:
Introduction: Verrucous hyperplasia (VH) is an oral potentially malignant disorder (OPMD). It can present in two forms: 1) Mass-type: an exophytic, fleshy verruca papillary outgrowth with a white and/or pink surface colour or 2) plaque type: a white, plaque-like verrucous lesion. 5-year malignant transformation rate is 10%. Verrucous carcinoma (VC) clinically resembles the exophytic, fleshy verruca mass typed VH. The two lesions may occur concurrently, and VC can develop from VH. VC is a low-grade variant of squamous cell carcinoma (SCC). It does not metastasize to lymph nodes or distant sites. VC has been found to have a 20% malignant transformation rate. S100A7 is a promising biomarker in early detection for oral squamous cell carcinoma (OSCC). It has been shown to play a role in modulating the p38 mitogen-activated protein kinases (MAPK) and RAB2A signaling pathway in vitro. Straticyte TM test is a method to quantify the expression of S100A7 and provide a quantitative model for prediction of risk of OSCC from pre-malignant lesions. Mcm-2 and geminin are DNA licensing proteins that are present in the cell cycle. Mcm proteins form a pre-replicative complex that acts as a license permitting DNA replication. Geminin is a proliferation marker that is present from G1-S transition to early M phase. These are all promising biomarkers for early detection of OPMD such as VH and VC progression to OSCC. Early diagnosis can improve patient morbidities and reduce the high mortality rates of OSCC.

Methods: A retrospective review of the department of pathology and laboratory medicine's archives is completed to examine patients 'histological slides with a diagnosed of VH and VC from January 1st, 2006 until January 1st, 2016. Immunostaining of the formalin-fixed paraffin embedded tissues (FFPE) with antibodies against S100A7, Mcm-2 and geminin. Straticyte TM test will be used to quantify the expression of S100A7 and provide a quantitative model for prediction of risk of OSCC from VH.

Hypothesis: We hypothesize that S100A7 levels are elevated in the epithelium of Verrucous Hyperplasia (VH) and Verrucous Carcinoma (VC) that transformed to Oral Squamous Cell Carcinoma (OSCC).

Discussion: No studies have looked at S100A7 expression in VH and VC. The data from this study will help guide future clinical decision making in the treatment of VH and VC to help improve patient outcomes and reduce patient morbidity and mortality.

Research theme 1: Cancer Biology
Research theme 2: Oral Biology and Medicine
Research theme 3:

Presenter's Name: Daniel, Maria

Additional Author(s): Kawa DT, Jackson-Boeters L, Betts D, Kiser P

Abstract Title: Exploring the Role of the Adaptor Protein p66Shc on Murine Embryonic Stem Cell Differentiation and Maturation

Abstract: Embryogenesis is a complex developmental process that relies on mechanisms of cell proliferation, signaling, and differentiation mediated by molecules such as adaptor proteins. When these mechanisms are interrupted, embryo pathologies occur. The general developmental role of the p66Shc adaptor protein on cell fate and maturation of the neuroectoderm germ layer has been explored. However, more research is required to expand on that role for different stages of maturity within a germ layer. To address this knowledge gap, I conducted a research project that aims to determine if p66Shc knockout (KO) causes maturation arrest in cells, and if it plays a role on maturation of ectoderm lineage derivatives other than the neuroectoderm. The methodology of this experiment built on previous research. We used Cell Lineage Identification RT^2 Profiler PCR Arrays to quantitatively analyze teratomas that were previously generated in vivo with wild type and p66Shc KO mouse embryonic stem cell injection in immunodeficient mice (Betts). Immunohistochemistry, hematoxylin staining, and in vitro qualitative analysis were also performed. By correlating immunohistochemistry with observed cellular morphological changes in the KOs, we hypothesize that the maturation state of the observed cell sets can be identified and are affected by p66Shc KO. This research is currently in progress, but its results will be available prior to the research poster submission deadline. It is expected that hematoxylin and eosin analysis will result in the WT teratomas characterized by well differentiated cells and the p66Shc KO teratomas characterized by poorly or undifferentiated cells. For immunohistochemical analysis, it is expected that the undifferentiated p66Shc KO cells will not be pluripotent but rather have committed to a germ lineage. After immunohistochemical analysis of the neuroectoderm-excluding ectoderm maker, it is possible for the p66Shc KO cells to be committed to the neuroectoderm or another ectoderm derivative. These results will expand on p66Shc's known role on cell differentiation and maturation. This can help understand how embryo pathologies arise. To enhance our understanding of both embryogenesis and its pathologies and explore improved knowledge translation in future approaches, the One Health approach will be applied to the results to address stakeholders outside academia and the influence of the animal, human, and environmental health pillars on this topic.

Research theme 1: One Health
Research theme 2:
Research theme 3:

Presenter's Name: Hazeema

Additional Author(s): Frisbee S

Abstract Title: Bridging the Gap: Insights from a Scoping Review on Reducing Hypertension Control Disparities in Primary Care Settings

Abstract:
Introduction: In the last decade, stakeholders overseeing hypertension (HT) control guidelines at national and international levels have underscored the significance of prioritizing marginalized communities. Recommendations for addressing HT control disparities and enhancing primary care have been published. Despite these efforts, the persistent low rate of controlled HT in these populations prompts an inquiry into the implementation, components, and effectiveness of targeted interventions in primary care settings.

Methods: A scoping review following the PRISMA-ScR Checklist is currently underway. Using a comprehensive search string, 1012 relevant empirical studies were identified from Scopus, PubMed, CINAHL, and Embase. As of now, 607 studies have undergone screening, with 25 meeting the eligibility criteria. Eligible studies are primary full-text research papers, published in the past 5 years, detailing interventions for adults diagnosed with HT from underserved or marginalized communities seeking care in primary care settings. These interventions focus on improving HT control, with reported outcomes comprising mean changes in blood pressure and/or shifts in the proportion of patients achieving controlled HT.

Results: Data from 17 of 25 eligible studies, with participant counts ranging from 16 to 3658, reveal the use of various intervention components such as home blood pressure monitoring (HBPM), web-based HT education applications, patient-centered lifestyle coaching by Community Health Workers, and medication prescription and adjustment by pharmacists using predetermined algorithms. The majority of these studies highlight a significant and immediate decrease in systolic blood pressure among hypertensive patients after the intervention, with sustained positive effects in subsequent follow-ups.

Discussion: Complex multi-component interventions, limited in feasibility and acceptability, may not be imperative for improving HT in marginalized populations. Focusing on cost-effective intervention elements, such as web-based HT education applications and HBPM directly integrated with the patient's electronic health record, appears sufficient for effective HT control. A stakeholder analysis will be conducted to identify the major stakeholders involved in environmental and animal topics relevant to this research project. Subsequently, an effective One Health approach aimed at mitigating HT control disparities at a population level will be discussed.

Research theme 1: Cardiovascular, Respiratory Health, and Metabolic Diseases
Research theme 2: One Health
Research theme 3:

Presenter's Name: Quan, Trinity

Additional Author(s): Kum J

Abstract Title: Developing a Histopathological Atlas of Laboratory Mouse Tissues as an Open Educational Resource

Abstract: The COVID-19 pandemic has exponentially accelerated a change in the methods by which education is delivered. With almost 1.2 billion students out of the classroom during the pandemic, there was a global shift toward virtual learning with increased use of online resources, including open educational resources (OERs). OERs are learning, teaching, and research materials available in the public domain, allowing for no-cost access and use.

Mouse models play a pivotal role in research as they offer insights into disease mechanisms and help to predict therapeutic actions. Currently, virtual microscopy and mouse atlas resources that are open access are quite limited, creating barriers for researchers and trainees in accessing these educational resources. Therefore, our study aims to create a histopathological atlas of laboratory mouse tissues as an OER.

To develop the histopathological atlas of the mouse tissues, we explored the use of Movat pentachrome stain for the histological visualization of collagen, elastin, muscle, mucin, and fibrin. As the pentachrome stain remains less explored compared with the widely used hematoxylin and eosin (H&E) stain, we will also include a comparison of the structures seen in both of these stains. Our comparative analysis of the two stains will help to determine if the pentachrome stain reveals additional key elements that may be undetected in the H&E stain. Specifically, we will explore the tissues from the eye, lung, liver, kidney, heart, tibia and femur of C57BL/6 mice. These stained tissue slides will be digitally scanned and analyzed to describe the tissue histology, anatomy, and physiology observed with the pentachrome stain compared to the H&E stain. We will then summarize these observations and will provide high-quality histological images of the various mouse tissues as an OER.

The goal of this project is to develop a histopathological atlas of laboratory mouse tissues available in the public domain in collaboration with other researchers exploring various disease models and staining techniques. By creating this OER, our study will contribute to the global shift towards accessible education, foster collaborative research, and provide a histopathological atlas for open science research and educational use.

Research theme 1: Digital Pathology
Research theme 2: Research in Education
Research theme 3: Test Utilization, Optimization and Quality Assurance

Presenter's Name: Conant, Gwendolyn

Additional Author(s): Cecchini M

Abstract Title: Introduction to grossing using standardized simulated specimen models

Abstract:
Introduction: Mistakes are an important part of learning but can pose concerns when working on critically important diagnostic specimens. However, it is crucial that Pathologists' Assistant (PA) students learn the practice of surgical pathology over a short time frame. To help build confidence and create a safe learning environment, simulated specimens could be safely utilized to mimic various grossing tasks. In the present study, we have attempted to generate a novel innovative method for teaching the basics of pathology grossing using simulated specimens. We hypothesize that alginate can be utilized to simulate various organs to aid in building foundational knowledge and skills that are essential for gross surgical pathology.

Methods: To test this hypothesis, we first utilized various ratios of water and alginate evaluate if the density and texture could mimic various gross organs. We then ensured our alginate models would be standardized and replicable by creating silicone molds for the thyroid, uterus, and prostate. We experimented with different materials to replicate mass or lesions within the alginate models. Finally, we presented our models to 5 Pathologists' Assistants, collected anonymous feedback, and updated our models accordingly.

Results: Our results demonstrate that alginate organ models are an effective tool to simulate grossing. 3 out of the 5 PA's strongly agree that the thyroid, uterus, and prostate alginate models would provide valuable practice experience for new students and would like to see these models integrated into the PA student program. Alginate models are inexpensive, produced within minutes, nonhazardous, and do not require specialized equipment. They are anatomically correct with excellent section quality and can be inked. Malignancies can be simulated, allowing for complex gross descriptions including measurements to resection margins.

Discussion: Our preliminary study finds that alginate can be effectively utilized as a simulated specimen in a safe learning environment. This will allow for assessment of students in terms of section quality, gross description, and overall comprehension of grossing tasks. These specimens may also be used to teach medical students and junior residents

Research theme 1: Research in Education
Research theme 2:
Research theme 3:

Presenter's Name: Nunes, Timothy

Additional Author(s): Nygard KL, Courchesne MCJ, Morris LE, McKenzie CA, Richardson BS, Delhaes F, Regnault TRH, Kiser PK

Abstract Title: Lifelong maternal Western Diet negatively impacts placental metabolome and placental vascularization, independent of BMI

Abstract:
Introduction: Independent of body mass index (BMI), a "Western Diet" (WD) high in refined sugars and saturated fats contributes to poor metabolic health. Maternal WD is associated with adverse pregnancy outcomes—including altered placental development. Studies investigating the impact of WD in normal-weight pregnant populations are limited, despite the increasing prevalence of metabolically unhealthy normal-weight persons. To elucidate the BMI-independent effects of WD on fetoplacental development, we utilized a non-obese WD guinea pig pregnancy model. We hypothesized that lifelong maternal WD would alter the placental metabolome in conjunction with impaired placental vascularization.

Methods: In-house-bred Dunkin-Hartley guinea pig sows were weaned onto control diet (CD) or WD and mated to CD boars at nine-months, then necropsied at 42d or 62d gestation (term ~68d). Placental samples were subject to untargeted LC-MS metabolomics, with analysis performed in MetaboAnalyst 5.0. Placental cross-sections were examined by immunofluorescence microscopy to characterize fetal capillaries and maternal lacunae.

Results: Multivariate analysis revealed 98 differentially abundant metabolites between WD and CD placentae, with 3 commonly down at both 42d and 62d: stearidonic acid, 9-cis-retinoic acid, and geranic acid ($p<0.05$, FC>2). Pathway analysis revealed altered arachidonic acid and linoleic acid metabolism at both 42d and 62d ($p<0.05$, impact>0.5). WD pregnancies exhibited significantly decreased fetal-placental weight ratios at 62d ($p<0.001$). In placental labyrinths, maternal lacunae to fetal capillary area ratios were increased at 62d ($p<0.01$).

Discussion: Our findings indicate that specific alterations to the placental metabolome are associated with impaired placental vascularization, which may contribute to adverse gestational outcomes observed with WD pregnancies. Future studies are needed to elucidate the interplay of pro-angiogenic arachidonic acid-derived eicosanoids and anti-angiogenic n-3 metabolites in WD pregnancies. Our work could refine pregnancy risk assessments in clinical settings, as we highlight the importance of evaluating maternal lifestyle and metabolic health—rather than BMI alone.

Research theme 1: Cardiovascular, Respiratory Health, and Metabolic Diseases
Research theme 2:
Research theme 3:

Presenter's Name: Vytlingam, Kevin

Additional Author(s): Chahal S, Min W, Zheng X

Abstract Title: Preventing Alloimmune Rejection After Heart Transplantation Using Circular RNA ZMIZ1-Engineered Dendritic Cells

Abstract:
Introduction: Alloimmune rejection is a vital concern after organ transplantation. As a result, transplant patients require lifelong immunosuppression, which can lead to toxicity, infections, and cancer. For this reason, new interventions to induce donor antigen-specific immune tolerance are required.Dendritic cells (DCs) play an important role in determining whether a transplanted organ is tolerated. Tolerogenic DCs (Tol-DCs) promote allograft tolerance by preventing T cell activation and stimulating regulatory T cell (Treg) generation. Immunosuppressive agents have been shown to generate Tol-DCs in vitro; however, new molecules to optimize Tol-DC induction should be investigated. Circular RNAs (circRNA) could be an ideal candidate for DC immunomodulation because they have many reported regulatory functions, such as sequestering microRNA and stabilizing protein interactions. Previous microarray data from our lab found an upregulation of circular RNA ZMIZ1 (circZMIZ1) in Tol-DCs. For this reason, we hypothesize that circZMIZ1 is immunosuppressive, and thus, overexpressing circZMIZ1 in DCs will promote a tolerogenic phenotype, conducive to improving allograft tolerance after heart transplantation.

Methods: We will overexpress circZMIZ1 in DCs and assess its effect on DC phenotype based on the expression of co-stimulatory molecules and both pro- or anti-inflammatory cytokines via flow cytometry. We will assess T cell activation and Treg generation using mixed lymphocytic reactions. We will employ a mouse heart transplant model and treat transplant recipient mice with circZMIZ1-engineered DC vaccines prior to heart transplantation. We will monitor graft survival time and examine histopathological features of the graft at endpoint.

Results: We expect to see increased Tol-DCs and immunosuppressive cytokines after circZMIZ1 overexpression in DCs. We also expect to see reduced T cell activation and increased Treg generation, all contributing to increased allograft tolerance. After heart transplantation, we expect to see increased graft survival time and decreased graft injury, inflammatory infiltrate, and fibrosis.

Discussion: Investigating circRNA as a modulator of DC phenotype and immunogenicity could contribute to the development of robust Tol-DC vaccines for preventing alloimmune rejection after organ transplantation.

Research theme 1: Cardiovascular, Respiratory Health, and Metabolic Diseases
Research theme 2: Infection, Immunity, and Inflammation
Research theme 3: Regenerative and Transplantation Medicine

Presenter's Name: Twible, Carolyn

Additional Author(s): Zhang Q

Abstract Title: Characterizing hippocampal dentate gyrus involvement in temporal lobe epilepsy

Abstract:
Introduction: Hippocampal sclerosis (HS) is the most common pathology finding for drug-resistant temporal lobe epilepsy (TLE). HS is diagnosed by identifying pyramidal neuronal loss and gliosis in Cornu Ammonis (CA). Dentate gyrus (DG) is the critical entry point in to the hippocampus and possesses the unique function of adult neurogenesis. However, changes in DG are not emphasized in the current diagnostic criteria of HS. In this study, we will characterize the morphological and genomic features of the hippocampal DG in TLE patients and investigate the underlying epileptogenic mechanisms.

Methods: Twenty-one TLE surgical resection cases (14 HS, 7 no-HS) and 10 control cases (4 non-TLE epilepsy control, 6 non-epilepsy control) were included. QuPath software was used to perform morphometry analysis on the DG, including Delaunay mean, cellular density, nuclear size and circularity. The DG of 18 selected TLE cases were micro dissected and underwent gene expression profiling, using NanoString targeted panels (1400 genes, targeted Neuroinflammation and Glial Profiling panels). Histopathological diagnosis and post-operative outcome were included for clinicopathological correlation.

Results: 1) HS patients show a significant increase in granule cell (GC) spacing and decrease in GC density within the DG compared to no-HS patients. 2) Regardless of the clinical diagnosis, patients that achieved seizure freedom post-operatively (Engel outcome scale 1a) demonstrated an increase in GC spacing and decrease in GC density in comparison to patients without significant seizure reduction. 3) The DG of HS patients demonstrated significant complement system activation, increased gliosis (both A1 & A2 astrocytes), matrix remodelling, and apoptosis but a decrease in neurogenesis, GABAergic and glutametergic synapses, and neuronal populations.

Discussion: Dentate gyrus has distinct morphometric features and gene expression in TLE patients, suggesting an important role in epileptogenesis.

Research theme 1: Digital Pathology
Research theme 2: Pathobiology of Neurologic Diseases
Research theme 3:

Presenter's Name: Woo, Elissa

Additional Author(s): Cecchini, MJ

Abstract Title: Comparison of digital image analysis and light microscopy for identification of HER2-low breast cancer

Abstract: Previously, the focus of human epidermal growth factor receptor 2 (HER2) testing was to identify protein overexpression due to the availability of targeted therapy for treating HER2-positive breast cancers. Current guidelines for HER2 immunohistochemistry expression scores are 3+ and 2+/in situ hybridization (ISH) positive deemed as HER2-positive and 0, 1+ and 2+/ISH negative being HER2-negative. HER2-low (scores of 1+ and 2+/ISH negative) is not currently recognized as an official category, but publication of DESTINY-Breast04 study of the impact of trastuzumab deruxtecan presents the significance of distinguishing a true negative and HER2-low, with scores of 1+ and 2+/ISH negative. The subtle differences between a HER2-negative and HER2-low score. This study explores of the concordance of results between two digital platforms, Visiopharm HER-2 CONNECT APP and QuPath, and traditional manual review by a pathologist. Digital analysis has proven to be a valuable and efficient tool to help with biomarker analysis, this study aims to uncover the accuracy and efficiency of each method while reviewing historical HER2 classification of breast cancer cases in 2023 at London Health Sciences Centre. Approximately 500 cases will be tested across all three methods and the results will be compared with the historical score assigned to the specimen. The HER2 slides had been stained on the Dako Omnis (Agilent Technologies) and digitized along with the corresponding hematoxylin and eosin slide using a Grundium Ocus 40. Preliminary results affirm the suitability of the digital platforms for biomarker analysis, positing digital assessment as a valuable tool in accurately distinguishing HER2-negative from HER2-low cases, thus ensuring precise patient diagnostics and effective treatment strategies.

Research theme 1: Cancer Biology
Research theme 2: Digital Pathology
Research theme 3:

Presenter's Name: Khandwala, Zoya

Additional Author(s): Zakirova K, Dick F

Abstract Title: The role of the WNT signalling cascade on Epithelial-Mesenchymal Transition in High-Grade Serous Ovarian Cancer

Abstract:
Background: High-grade serous Ovarian Cancer (HGSOC) is an aggressive form of Epithelial Ovarian Cancer (EOC) characterized by atypia and pleomorphic nuclei. A defining characteristic of HGSOC is the cellular aggregates known as spheroids that form in the peritoneum during metastasis. These aggregates enter a dormant state wherein they are growth-arrested and unresponsive to therapy. Spheroid cells are suspected to possess qualities of both epithelial and mesenchymal cells. The formation of the hybrid cluster is attributable to Epithelial-Mesenchymal Transition (EMT). Some evidence suggests that EMT, a component of metastasis, is regulated by the WNT signalling pathway. The WNT pathway is thus far known to modulate other metastatic cell behaviours such as adhesion, proliferation, and fate in various cancers, EOC included. Given the existing and unknown information on WNT and EMT, we hypothesize that the WNT genes will promote epithelial-mesenchymal transition, spheroid survival, and ultimately metastasis.

Methods: The OvCar8 cell line will be used to establish an in vitro model for serous ovarian cancer, where control cells and WNT 8B/9B double-knockout cells will be followed. Initially, a primary tumor model will be created by allowing cells to adhere to tissue culture plates. Fixed numbers of cells will then be plated to ultra-low attachment plates to form spheroids that will incubate for seven days. EMT status will be analyzed by comparing RNA and protein expression of epithelial and mesenchymal cell markers such as cytokeratin and vimentin, respectively, through RT-qPCR and Western Blots of the adherent cells and 7-day spheroids. Furthermore, RT-qPCR will be used to examine RNA expression of EMT-regulating transcription factors Twist, SNAI1, and SNAI2.

Results: We expect that the WNT 8B and 9B double knock-out cells will show a shift in Epithelial and Mesenchymal balance. The double-knockout adherent and spheroid cells should be more epithelial, and thus should express more cytokeratin and less vimentin compared to the healthy control cells. Furthermore, the double-knockout cells should have lower expression of EMT-promoting transcription factors Twist, SNAI1 and SNAI2.

Discussion: Currently, the lack of existing research on spheroid dormancy and EMT in HGSOC contributes to high morbidity and mortality. This study attempts to identify the role of WNT 8B and 9B in Ovarian Cancer to develop therapies to improve patient prognosis.

Research theme 1: Cancer Biology
Research theme 2:
Research theme 3:

Presenter's Name: Han, Ji Hyun

Additional Author(s): Sabharwal A, Lovell J, Khan ZA, McCord C

Abstract Title: Osteomyelitis of the jaw: An investigational study of the clinicopathological features and pathogenesis of refractory vs non refractory osteomyelitis

Abstract:
Introduction: Osteomyelitis (OM) means inflammation/infection of the bone marrow. The initial source of infection can be caused by many different factors; however, this process continues to propagate until the source of infection has been removed. In recent years, there has been an increase in subset of patients, who present with clinically aggressive disease. Based on the classifications present in literature, we have classified the groups into Refractory (R) vs non refractory (NR) cases, with ROM patients requiring more than 1 surgical procedure after adequate initial management. We hypothesize that ROM patients are associated with specific bacteria/inflammatory markers that make them more clinically aggressive, associated with poor clinical outcomes, and demonstrate distinguishing clinicopathologic features. The objectives are to examine the clinical and histological characteristics of OM to determine if differences exist between the two groups.

Methods: A retrospective chart review of the records of patients diagnosed with OM in the OMFS departments of LHSC from Jan 1, 2002 until Jan 31, 2021 will be completed. Cases grouped according to their outcome; R vs NR. Initial confirmation of RNA isolation from formalin-fixed paraffin embedded tissues (FFPE) completed. Following this, FFPE obtained from patients from the retrospective chart review have been used to complete Immunohistochemistry (IHC) for TLR and MYD88 signaling. qPCR pending to assess for specific inflammatory factors. Prior to qPCR of official case samples, protocol is being developed to determine if we can isolate RNA or DNA from FFPE samples.

Results: The retrospective chart review included a total of 87 patients; 45 females and 42 males. Out of the 87 patients, 56 samples were determined to be OM. 8 R groups and 8 NR OM groups chosen for experimental portion. Initial RNA and DNA retrieval from FFPE soft tissue and bone revealed some positive samples. Further results are to be determined.

Discussion: Currently in the literature, very few studies examine the features of ROM compared to those with NROM. It is expected that a difference in microorganisms, inflammatory markers, as well as other environmental/personal risk factors of individuals will be seen in the refractory OM subset. The data from this study will help guide future clinical decision making in the treatment of ROM of the jaw to help improve patient outcomes and reduce patient morbidity.

Research theme 1: Infection, Immunity, and Inflammation
Research theme 2: Oral Biology and Medicine
Research theme 3:

Presenter's Name: Truong, Ivy

Additional Author(s): Rudak P, Cecchini M

Abstract Title: Optimizing the digital quantification of PD-L1 as a predictive marker for immunotherapy response

Abstract:
Introduction: PD-L1 is an established biomarker for predicting anti-PD-L1/PD-1 immunotherapy response in various cancers. Measuring PD-L1 expression can help with predicting patient response and prognosis, assessing whether immunotherapy is the most optimal treatment. Traditionally, the quantification by pathologists is a laborious and imprecise process of manual counting using a conventional microscope. Furthermore, biases and interpretations between pathologists result in varying reproducibility and accuracy with quantification, leading to an increased risk of inappropriate treatment. Integrating digital image analysis (DIA) can support pathologists in various diagnostic techniques and has shown promise in improving accuracy and reliability. We hypotheszie that DIA would improve the accuracy of biomarker quantification, specifically PD-L1, across various tumours for predicting immunotherapy response.

Methods: QuPath, an open-source digital image analysis software, was used for the analysis of whole slide images of gastric, and head and neck squamous cell tumors obtained from Canadian Biomarker Quality Assurance. A random-trees classifier will be trained on regions of interest, categorizing cells into tumour, immune, and stromal cell types, and applied to the whole tumour sample. Quantifying PD-L1 expression amongst the cell types allows calculation of combined positive score (CPS) and tumour proportion score (TPS), the standard scoring system for PD-L1 expression. Concurrent validity was assessed by comparing DIA and manual scores with ground truth data, determining accuracy of digital scoring.

Results: DIA was capable of detecting PD-L1-positive cells while also classifying them based on cell types. Furthermore, quantification yielded more reliable results, demonstrating greater agreement amongst intraclass scoring than manual assessment. Quantification using DIA demonstrated greater accuracy compared to visual scoring.

Discussion: DIA scoring demonstrated higher intraclass agreement, higher accuracy and precision, compared to visual scoring. Analysis using DIA provided insight into the barriers of scoring, such as staining patterns. Integrating DIA as a supportive tool for pathology lays the groundwork for creating a fully automatic machine-learning system capable of multiple diagnostic tasks across various whole slide images. DIA can potentially standardize biomarker quantification due to improved reproducibility in scoring amongst pathologists

Research theme 1: Digital Pathology
Research theme 2: Test Utilization, Optimization and Quality Assurance
Research theme 3:

Presenter's Name: Orsava, Jenna

Additional Author(s): Diao H, Taray-Matheson D, Vytlingam K, Min W

Abstract Title: The Interplay of Piezo1 and DLC1β in Cardiac-Ischemia Reperfusion Injury During Heart Transplantation

Abstract:
Introduction: Cardiac ischemia-reperfusion injury (IRI) occurs intraoperatively during heart transplantation and threatens the survival of the graft within the recipient. Previous experimentation in our lab has implicated DLC1β overexpression as one potential method of preventing the injurious effects of IRI. Another protein, Piezo1, may also be involved in cardiac IRI, as indicated by studies that have demonstrated its upregulation during myocardial injury; thus, manipulating its expression may be cardioprotective. It remains unknown however if this is true, and if it is, whether or not controlling Piezo1 can work synergistically with DLC1β to provide cardioprotective effects. Based on the literature review as well as previous data collected in our lab, we hypothesize that Piezo1 expression will increase in the context of cardiac IRI but can be counteracted by DLC1β, and that Piezo1 inhibition will lead to reduced cell death during IRI.

Methods: We will test this by culturing rat cardiomyocytes and exposing them to hypoxia-oxygenation reperfusion (H/OR) to determine how this may alter Piezo1 expression through changes in mRNA transcript and protein levels. We will also treat cardiomyocytes with either a mechanosensitive channel inhibitor (GSMTx4) or a Piezo1-specific activator (Yoda1), subject them to H/OR, and assess the effect of Piezo1 on cell death. Finally, we will also test the effect that DLC1β overexpression has on Piezo1 expression in cardiac grafts after heart transplantation.

Results: Our results show that in both rat cardiomyocytes and mice hearts, Piezo1 is upregulated after IRI. Treating rat cardiomyocytes with Yoda1 upregulated Piezo1 expression and increased the percentage of PI+ dead cells under IRI. Treatment with GsMTx4 however, decreases the expression of Piezo1 in cardiomyocytes and results in a decreased percentage of PI+ dead cells. Finally, treatment of cardiac grafts with DLC1β has demonstrated cardiac injury in IRI, which is related to the repressed expression of Piezo.

Discussion: These findings indicate that the increased expression of Piezo1 seen during IRI plays a role in the development of the injury, and inhibition of this molecule is cardioprotective, providing a potential pharmacological target for preventing graft rejection. Piezo1 inhibition and DLC1β overexpression may act synergistically together to reduce cell death during IRI, which needs further study.

Research theme 1: Cardiovascular, Respiratory Health, and Metabolic Diseases
Research theme 2: Regenerative and Transplantation Medicine
Research theme 3:

Presenter's Name: Sutherland, Janice

Additional Author(s): McKinley G

Abstract Title: A Qualitative Examination into the Factors that Influence Dog Walking: A One Health Approach

Abstract: Physical activity is associated with positive physical and mental health outcomes. Health Canada recommends that Canadian adults aim for 150 minutes per week of moderate-to-vigorous physical activity. Walking specifically dog walking is one form of physical activity that is cost-effective and can be done at a person's own pace and choice of time of day. Dog ownership is often associated with increased physical activity which translates into overall better health for the dog owner and dog; but not all dog owners walk their dogs and not all dog owners walk their dogs enough to meet the physical activity target of 150 minutes per week. In this study, a One Health perspective will be used to explore what factors influence dog walking. Secondly the interconnections among humans, animals, and the environment: specifically, the impact of built and social environment on dog walking will be done. This study will be utilizing a feminist qualitative description methodology to interview current dog owners in London and Middlesex surrounding area. The data from the interviews collected will be summarized using a qualitative content analysis. The summary will be integrated into the Dahlgren and Whitehead Model of health to identify which social determinants of health impact dog walking and to identify areas where policy can be developed to facilitate dog walking in London and Middlesex area.

Research theme 1: Cardiovascular, Respiratory Health, and Metabolic Diseases
Research theme 2: One Health
Research theme 3:

Presenter's Name: Lu, Haitao

Additional Author(s): Huang X, McLeod P, Jiang J, Steriopoulos J, Zhang Z

Abstract Title: The ZBP1-RIPK3 complex orchestrates PANopotosis to induce cell death and transplantation rejection by sensing cfDNAs

Abstract:
Background: Donor-derived cell-free DNAs (dd-cfDNAs) have emerged as potent triggers leading to transplant injuries and rejection after many reports claimed cfDNAs are the markers monitoring rejection. However, current reports have not illustrated the mechanisms of how cfDNAs induce cell death and graft injury during transplantation rejection. In this context, we would determine if and how cfDNAs lead to various death programs and aggravate transplantation rejection.

Method: We conducted cell death assays in cardiovascular endothelial cells to confirm whether cfDNAs induce cell death. Next, we would determine downstream molecules or effectors that mediate cell death by using protein-protein interaction technology, qRT-PCR, gene silencing, and western blotting to identify key molecules markers for pyroptosis, apoptosis or necroptosis respectively to determine the occurrence of PANoptosis (a crosstalk among pyroptosis, apoptosis and necroptosis). After confirming the form of cell death, we used gene knockout mice for heart transplantation. HE, TUNEL, IHC and survival test would be used to assess the role of gene knockout in heart transplantation.

Results: We found markedly elevated levels of cell death in endothelial cells treated with cfDNAs. Interestingly, PCR showed that ZBP1 was significantly increased. In addition, ZBP1 silencing reduced cell death and ZBP1 interacts with RIPK3. The ZBP1-RIPK3 complex activated multiple molecules, including GSDMD, caspase 3 and MLKL, to initiate PANoptosis. In vivo, HE and TUNEL showed reduced positive intensities from heart grafts of ZBP1 KO transplant mice compared to WT grafts. IHC demonstrated the drops of PANoptosis markers and inflammatory molecules from ZBP1 KO mice grafts compared to WT grafts. Additionally, an increase in the days of post-transplantation survival also supported that ZBP1 KO attenuates high lethality resulting from transplant injuries.

Conclusion: cfDNAs induce cell death and aggravate transplant injuries by activating ZBP1. ZBP1 then interacts with RIPK3 to initiate PANoptosis. ZBP1's knockout effectively attenuated PANoptosis-caused injuries during heart transplantation. Therefore, ZBP1 knockout might be an effective strategy to modulate inflammation and improve heart allograft rejection.

Research theme 1: Cardiovascular, Respiratory Health, and Metabolic Diseases
Research theme 2: Regenerative and Transplantation Medicine
Research theme 3:

Platform Presentations
Session 1
1:00 p.m. - 2:00 p.m.

#	Time	First Name	Last Name	Title
1	1:00 p.m.	Peter	Zeng	Resolving the clinical, genetic, and cellular landscapes of subglottic stenoses
2	1:15 p.m.	Komila	Zakirova	Netrin signaling supports spheroid dormancy and metastatic spread in HGSOC
3	1:30 p.m.	Rober	Abdo	The Spatial Transcriptomic Landscape of Breast Cancer Brain Metastasis
4	1:45 p.m.	Megan	Hong	Impact of intratumoural macrophages on anti-CTLA-4 efficacy and anti-PD1 resistance in neuroblastoma tumours with induced DNA mismatch repair deficiency

Presenter's Name: Zeng, Peter

Additional Author(s): Lin J, Fung K, Khan H, Cecchini MJ, Hu A, MacNeil D, Mendez AI, MacInnis P, Karimi A, Ying S, Al Jawhri MW, Lin S, Shaikh M, Pan N, Jarycki L, Wen R, Coburn B, Mymryk JS, Inculet R, Barrett JW, Nichols AC

Abstract Title: Resolving the clinical, genetic, and cellular landscapes of subglottic stenoses

Abstract: The larynx is divided into the supraglottis, glottis, and subglottis, which each have complex tissue niches with important differences in tissue composition, lymphatic drainage, and ability to counter infections and respond to injuries. First described in 1972, idiopathic subglottic stenosis (iSGS) is a devastating orphan disease characterized by recurrent and progressive scarring of the lower laryngeal and upper tracheal airway with unknown cause. Scarring leads to narrowing of the breathing passage and potentially life-threatening dyspnea in otherwise healthy individuals. Intriguingly, the disease is almost exclusively restricted to Caucasian females of reproductive age. We leveraged our national health care system of laryngology practice, which has allowed us to for the first time prospectively investigate human subglottis and epiglottis at the clinical, cellular, genetic, and molecular level. We prospectively collected 92 diseased subglottic tissue and 89 unaffected supraglottic tissues (biopsies from the tip of the epiglottis) from iSGS patients) through surgical biopsy and rapid sample preservation. We deciphered the single-cell taxonomy of the human subglottis and epiglottis using single-nucleus sequencing in both healthy and disease states. We then leveraged the largest bulk transcriptomic study in laryngology that allowed us to correlate cell type abundance with clinical covariates, such as sex, age, BMI, smoking status, and most importantly clinical outcomes. Furthermore, we developed, to the best of our knowledge, the first biomarker associated with recurrent relapse in iSGS. We discover the presence of epithelial and fibroblast progenitor subsets within the healthy subglottis that are less frequent within the epiglottis, which is anatomically adjacent tissue. The uncontrolled proliferation of these cell subsets may orchestrate a fibroinflammatory cascade following injury or other as yet unknown stimulus. In addition, we discover the subglottic microenvironment in iSGS patient is changing dynamically both with or without therapeutic intervention with longitudinal sampling. Finally, we identify germline genetic variants driving subglottic microenvironmental differences. Our findings have important implications for the design of clinical investigations using targeted therapies or immunotherapeutic approaches that target a specific cell population. Taken together, our results may further precision laryngology and ultimately improve patient outcome.

Research theme 1: Bioinformatics and Data Science
Research theme 2: Cardiovascular, Respiratory Health, and Metabolic Diseases
Research theme 3: Infection, Immunity, and Inflammation

Presenter's Name: Zakirova, Komila

Additional Author(s): MacDonald J, Passos DT, Dick F

Abstract Title: Netrin signaling supports spheroid dormancy and metastatic spread in HGSOC

Abstract:
Introduction: Metastasis in ovarian cancer is confined to the peritoneal cavity, where tumor cells form multicellular clumps known as spheroids. Spheroid cells enter a dormant state by ceasing proliferation and can go undetected during surgical debulking and persist after chemotherapy. Understanding the biology of spheroid cell dormancy and its chemoresistance is crucial for developing effective therapies to prevent cancer recurrence.

Methods: We identified Netrin signaling as being essential for the survival of dormant spheroids. Netrins are a family of secreted molecules that act as guidance cues during formation of the nervous system. Previous studies have implicated Netrins in the development of various cancers, however its role in the pathobiology of ovarian cancer is yet to be explored. We demonstrated that overexpression of Netrin-1 or -3 ligands enhanced spheroid formation in an in vitro model system of cellular dormancy. Xenograft experiments in immunodeficient female mice revealed that overexpressing Netrin-1 and -3 leads to increased metastatic dissemination in vivo. Conversely, mice injected with cells lacking Netrin signaling, achieved through genetic deletion of UNC5 receptor homologs, showed significantly prolonged disease-free survival compared to the control group.

Results: We found MEK and ERK as downstream targets of Netrin-mediated cell survival in dormant conditions. Ovarian cancer spheroid cells showed ERK activation in response to stimulation with recombinant Netrin-1. Viability of ovarian cancer dormant spheroids was greatly compromised by MEK inhibitors, further suggesting that Netrin signaling regulates survival through MEK and ERK activation. Similarly, knockout of UNC5 family of receptors blocks ERK activation and inhibits Netrin-mediated survival of spheroid cells. This suggests Netrins signal through UNC5 receptors to activate ERK to support dormant cell survival. Moreover, treatment of xenografted mice with the MEK inhibitor Trametinib resulted in reduced metastatic spread to vital organs and significantly fewer viable spheroids recovered from the peritoneal cavity compared to the vehicle treated group.

Significance: Our findings indicate that Netrin signaling plays a crucial role in the pathobiology of ovarian cancer and may represent a promising target for new therapies to combat metastatic relapse. More research is necessary to fully comprehend how Netrins regulate spheroid cell dormancy and survival in ovarian cancer.

Research theme 1: Cancer Biology
Research theme 2:
Research theme 3:

Presenter's Name: Abdo, Rober

Additional Author(s): Li SS, Zhang Q

Abstract Title: The Spatial Transcriptomic Landscape of Breast Cancer Brain Metastasis

Abstract:
Background: Brain metastases (BrM) represent a leading cause of cancer mortality, exhibiting notorious resistance to treatment despite advances in systemic therapies. Breast cancer is one of the most common primary tumors for brain metastasis. The unique brain tumor microenvironment (BTME) further complicates the challenges associated with treating brain metastases.

Methods: We identified 34 cases of patient-paired surgically resected brain metastases with a breast origin. Additionally, six cases of non-tumoral brain controls were included. Two tissue microarray (TMA) blocks were constructed. NanoString GeoMX Digital Spatial Profiling (DSP) using the whole-transcriptome atlas (WTA) was employed. For each patient, three ROIs were analyzed: primary breast cancer (BC), metastatic tumor cells (MTC), immediate brain microenvironment (BTME). Furthermore, proteomics and phosphotyrosine profiling were conducted on the primary triple-negative breast cancer (TNBC) cell line (4T1) and its metastatic-brain tendency derivatives (4T1-BrM5) using tandem mass tag (TMT) labeling and SH2 superbinder agarose beads methods.

Results: 1) Analysis of the PAM50 gene signature revealed almost half of primary breast cancer cases change molecular subtypes at their matched brain metastatic sites. Interestingly, nearly all luminal A shifted to luminal B and HER-2 enriched subtypes. The majority of the triple negative BC, however, remained the same genotype at the metastatic site. 2) BTME exhibited cellular and molecular plasticity characterized by three distinct subtypes (BTME 1-3) identified through unsupervised clustering. These BTME subtypes were independent of the anatomical locations of BrM or the PAM50 profile of their corresponding MTC. The "neural-like" BTME-3 shared signaling pathways with non-tumoral brain controls, exhibited the slowest homing of BrM. Patients with BTME-3 demonstrated the longest survival. On the other hand, patients with "fibro genic" BTME-1 is distinguished by an abundance of tumor-facilitating endothelial and myeloid cells, while BTME-2 exhibits rich glutamatergic signaling and shortest survival. 3) Integrated proteomics and phosphotyrosine analysis on the cell lines identified an enrichment of the FAK-AKT-mTORC1 axis in 4T1-BrM5.

Conclusion: This study provides transcriptomic evidence of breast cancer plasticity during brain metastasis, highlighting significant remodeling of the brain microenvironment to accommodate metastatic breast cancer cells.

Research theme 1: Bioinformatics and Data Science
Research theme 2: Cancer Biology
Research theme 3:

Presenter's Name: Hong, Megan

Additional Author(s): Figueredo R, Maleki Vareki S

Abstract Title: Impact of intratumoural macrophages on anti-CTLA-4 efficacy and anti-PD1 resistance in neuroblastoma tumours with induced DNA mismatch repair deficiency

Abstract:
Introduction: Immune checkpoint inhibitors (ICIs) such as anti-PD1 and anti-CTLA-4 enhance patients' anti-tumour immune responses to eliminate cancer cells. ICIs have revolutionized the treatment of cancer in the last decade; however, their efficacy is limited to a small subset of patients. The DNA mismatch repair (MMR) pathway corrects mismatched base pairs that occur during DNA replication. Notably, patient response to anti-PD1 therapy is positively associated with those with MMR-deficient (dMMR) tumours in several cancers. Although anti-PD1 is approved for these patients, more than half do not respond, highlighting the need to understand mechanisms of resistance to provide alternative therapeutic approaches. We have previously shown that inducing MMR deficiency in an ICI-refractory and MMR-proficient (pMMR) neuroblastoma model renders tumours sensitive to anti-CTLA-4 therapy, but they remain unresponsive to anti-PD1 therapy. This study investigates how induced MMR deficiency modulates the tumour immune microenvironment and examines immune mechanisms driving anti-PD1 resistance and anti-CTLA-4 sensitivity in neuroblastoma tumours.

Methods: MMR repair deficiency was induced in the murine neuro-2a cell line by knocking out Mlh1 expression using CRISPR/Cas9. pMMR or dMMR tumours were grown in immunocompetent syngeneic A/J mice and were treated with anti-CTLA-4 or anti-PD1 once tumours were palpable. Targeted immune cell populations were depleted to assess their effects on ICI response. Tumour growth was measured followed by immunophenotyping of tumours and spleens by flow cytometry.

Results: Induced MMR deficiency in neuro-2a tumours significantly increased the presence of pro-inflammatory (Ly6cHigh) and anti-inflammatory (Ly6cLow) macrophages compared to pMMR tumours. Preliminary data suggest that depletion of macrophages in dMMR tumours can sensitize them to anti-PD1 therapy. In contrast, anti-CTLA-4 efficacy in dMMR tumours depended on Ly6cHigh macrophages that depleted regulatory T-cells through Fc-dependent mechanisms.

Discussion: These results suggest that while the presence of macrophages in dMMR tumours can render tumours resistant to anti-PD1 therapy, they can be leveraged to improve the efficacy of Fc-dependent therapeutics such as anti-CTLA-4. In conclusion, understanding tumour immune microenvironment features that facilitate response to ICIs will enable us to choose therapeutics strategically, ultimately optimizing patient outcomes.

Research theme 1: Cancer Biology
Research theme 2: Infection, Immunity, and Inflammation
Research theme 3:

Platform Presentations
Session 2
2:15 p.m. - 3:00 p.m.

#	Time	First Name	Last Name	Title
1	2:15 p.m.	Melissa	Menard	Quantifying Mismatch Repair Immunohistochemistry (MMR IHC) Using Digital Pathology in Colorectal Specimens
2	2:30 p.m.	Jacob A.	Houpt.	Efficacy of Routine Scout Sections in the Diagnosis of Spongiform Prionopathies
3	2:45 p.m.	Hao	Li	Validation and Application of BRAF V600E Immunohistochemistry in Central Nervous System (CNS) Tumours

Presenter's Name: Menard, Melissa

Additional Author(s): Grinrod N, Cecchini M, Wehrli B

Abstract Title: Quantifying Mismatch Repair Immunohistochemistry (MMR IHC) Using Digital Pathology in Colorectal Specimens

Abstract:
Introduction: Colorectal cancer represents a significant global health burden and is particularly prevalent in Western countries. A subset of cases is attributable to deficiencies in mismatch repair (MMR) genes, the detection of which is crucial for directing appropriate therapy. Immunohistochemical staining using the chromogen 3,3′-diaminobenzidine (DAB) is commonly employed to detect tumors with loss of MMR protein expression. However, interpretation of this test is subjective, and the staining quality may be compromised by suboptimal tissue fixation. This study aims to establish a quantitative threshold for MMR protein expression by immunohistochemical staining in colorectal cancer cases to enhance the objectivity and reliability of the interpretation of immunohistochemical staining for MMR protein expression.

Methods: Immunohistochemical staining results for MMR proteins on the initial biopsy and the subsequent resection of 49 colorectal cancers specimen were analyzed using QuPath software to determine comprehensive cell detection, tumor-stroma classification, and for the quantification of DAB staining intensity in tumor and stromal components.

Results: Cases with intact MMR protein expression exhibited an average ratio of DAB staining intensity in tumor to stroma of 3.76, while cases with loss of MMR proteins showed an average ratio of 0.40. A proposed objective cutoff value of <1 indicates loss of MMR expression, while >1 suggests intact expression, with a potential equivocal range. This approach could be integrated into a semi-automated machine learning workflow for MMR testing, promising improved efficiency, and accuracy in pathology practice.

Discussion: Establishing a quantitative threshold for MMR staining in colorectal cancer holds significant clinical implications, facilitating more objective and standardized interpretation of immunohistochemistry results. Integration of this approach into semi-automated workflows has the potential to streamline MMR testing, ensuring more consistent and accurate identification of cases with MMR deficiencies, thus enabling tailored therapeutic strategies and enhanced management of colorectal cancer patients. A next step is to investigate the impact of fixation times on MMR IHC staining intensity.

Research theme 1: Cancer Biology
Research theme 2: Digital Pathology
Research theme 3:

Presenter's Name: Houpt, Jacob A.

Additional Author(s): Ang LC

Abstract Title: Efficacy of Routine Scout Sections in the Diagnosis of Spongiform Prionopathies

Abstract:
Prionopathies are a rare group of CNS diseases defined by aggregation of misfolded prion protein (PrP), and include sporadic, iatrogenic, and familial types of Creutzfeldt-Jakob disease (CJD), variant CJD, kuru, other genetic forms such as Gerstmann-Straussler-Scheinker disease (GSS), and variably protease-sensitive prionopathy (VPSPr). Due to their anticipated risk of infectivity, advanced precautions are undertaken in centres handling possible prionopathy cases, and certain centres take limited sampling (scout sections) in order to render a preliminary diagnosis before referring the brain to a subspecialized centre with dedicated equipment and resources. In Canada, this is undertaken by the Creutzfeldt-Jakob Disease Surveillance System (CJDSS), which receives all such cases nationwide.

Even the limited sampling of scout sections (ex: frontal cortex, temporal cortex, and cerebellar vermis) demand an intensive resource commitment. Therefore, it is of interest to examine the accuracy of the neuropathological evaluation of scout sections against the diagnosis rendered by the CJDSS. In the London Health Sciences Centre database, there were 111 completed referrals: 88 were positive for a prionopathy (86 sporadic/iatrogenic/familial CJD, 1 GSS, and 1 sporadic panencephalic CJD) and 23 had no evidence of a prionopathy (all 23 of which were correctly identified as such). Of the 88 confirmed cases, 6 were preliminarily suspicious for CJD with notable uncertainty, due to equivocal PrP immunohistochemistry (IHC), concomitant neurodegenerative diseases, and/or lack of histological findings with clinical suspicion of disease involvement contralateral to the side sampled. The scout sections, as expected, were not capable of distinguishing rarer prionopathies (ie. GSS and sporadic panencephalic CJD) from the more typical cases.

In some CJD cases, extensive vacuolar changes were relied upon in place of unreliable PrP immunopositivity. Frontal and temporal cortices were often co-involved, though with occasional differences in PrP IHC intensity. In several cases, there was isolated involvement of the vermis by IHC-positive plaques and unremarkable neocortices, supporting the necessity of cerebellar inclusion in routine sampling. Overall, scout samples demonstrate considerable efficacy in the diagnosis and triaging of suspected prionopathy cases, though with some limitations incurred in artifactual immunostaining, multiple disease processes, and rarer prionopathies.

Research theme 1: Pathobiology of Neurologic Diseases
Research theme 2: Test Utilization, Optimization and Quality Assurance
Research theme 3: Infection, Immunity, and Inflammation

Presenter's Name: Li, Hao

Additional Author(s): Wehrli B

Abstract Title: Validation and Application of BRAF V600E Immunohistochemistry in Central Nervous System (CNS) Tumours

Abstract:

Introduction: BRAF is a proto-oncogene involved in the MAPK/ERK signal transduction pathway. In the central nervous system (CNS), there is frequent histological overlap amongst different tumour entities. However, some tumours, especially those in the pediatric and adolescent / young adult populations, are driven by a BRAF V600E point mutation, and identifying its presence in a tumour may assist in diagnosis. Currently, the gold standard method of mutation identification is next-generation sequencing (NGS), which is costly and has a relatively long turn-around-time. Immunohistochemistry (IHC) with an antibody targeting the mutant protein is an alternative assay which may eliminate these limitations. In this quality improvement/assurance study, we present preliminary data on whether IHC for BRAF V600E can reliably identify the mutation in formalin-fixed paraffin-embedded CNS tumour tissue.

Methods: We retrospectively retrieved cases of CNS tumours from June 2021 to December 2023, which were tested with IHC for BRAF V600E (clone VE1, Abcam, 1:100) followed by NGS confirmation. We compared the results of IHC vs. NGS, and additionally analyzed the quality of IHC staining.

Results: There were 13 eligible CNS tumour cases during the time period analyzed, with NGS confirming 5 positive and 8 negative cases. The patient age ranged from 3 to 26 years for the positive cases, and 4 to 73 for the negative cases. The diagnoses were 9 gliomas of various types, 3 glioneuronal tumours, and 1 craniopharyngioma. The IHC results (positive vs. negative) reported by the signing pathologist aligned with the NGS in all cases. The staining quality of 1 positive case was diffuse and strong, while the others were focal to patchy and weak to moderate. In 2 cases deemed negative, there was very focal weak staining.

Discussion: While our preliminary results demonstrate an 100% sensitivity and specificity for IHC to identify the BRAF V600E mutation in formalin-fixed paraffin-embedded CNS tumour tissue as interpreted by the signing pathologists, the staining quality in some cases may be interpreted as equivocal. Future directions, in addition to analyzing more cases, include analyzing intra- and inter-observer variability in IHC interpretation with optimization of the staining protocol as needed.

Research theme 1: Cancer Biology
Research theme 2: Pathobiology of Neurologic Diseases
Research theme 3: Test Utilization, Optimization and Quality Assurance

NOTES

NOTES

PATHOLOGY AND LABORATORY MEDICINE

RESEARCH DAY 2024

Schulich MEDICINE & DENTISTRY

London Health Sciences Centre

Western