

A background image of laboratory glassware, including test tubes and a pipette, with a blue and yellow bokeh effect.

**RI-MUHC
2024
Summer Student
Research Day**

**Journée de la
recherche des
étudiants d'été
2024 de
l'IR-CUSM**

**Wednesday
August 14, 2024
8:15a.m. to 4:00 p.m.**

**Mercredi
14 août 2024
8 h 15 à 16 h 00**

Chère communauté de l'IR-CUSM,

Nous vous souhaitons chaleureusement la bienvenue à notre très attendue journée annuelle de la recherche des étudiants d'été de l'IR-CUSM ! Cette année, nous sommes fiers de présenter votre passion pour l'apprentissage et l'innovation. Au total, nous avons reçu 118 résumés des 8 programmes de recherche de l'IR-CUSM – dont 16 présentations orales programmées et 102 présentations par affiches tout au long de la journée. Votre dévouement à l'excellence académique et votre enthousiasme à partager vos recherches, vos projets et vos idées avec notre communauté ont fait de cet événement un moment vraiment spécial. Les étudiants d'été ont travaillé dur tout au long de l'été et c'est l'occasion pour eux de partager les résultats de leurs recherches avec tous les membres de l'IR-CUSM. Notre objectif est de créer un environnement d'apprentissage inclusif et stimulant dans lequel de nouvelles idées peuvent être échangées et de nouveaux liens peuvent être établis. Tout le monde est invité à s'engager avec des pairs partageant les mêmes idées et provenant de différents domaines. Saisissez cette occasion d'élargir vos horizons, d'échanger des idées, de poser des questions, de vous encourager et de favoriser des collaborations durables. L'événement de cette année promet d'être inoubliable.

Nous espérons que vous apprécierez les présentations et nous nous réjouissons de vous accueillir.

Le comité d'organisation

Dear RI-MUHC community,

We extend a warm welcome to each one of you to our highly anticipated annual RI-MUHC Summer Student Research Day! This year, we are proud to showcase your passion for learning and innovation. In total, we received 118 abstracts from the 8 RI-MUHC research programs - with 16 oral presentations scheduled and 102 poster presentations throughout the day. Your dedication to academic excellence and your enthusiasm for sharing your research, projects, and ideas with our community have made this event a truly special occasion. Summer students have been hard at work over the summer and this is their opportunity to share their research findings with everyone at the RI-MUHC. Our goal is to create an inclusive and stimulating learning environment in which new ideas can be exchanged and new connections can be made. Everyone is welcome to engage with like-minded peers from various fields. Embrace this chance to expand your horizons, exchange insights, ask questions, provide encouragement, and help foster lasting collaborations. This year's event promises to be unforgettable.

We hope you enjoy the presentations and look forward to welcoming you.

The Organizing committee

Emily Bell, Ariel de Roo, Marie-Claude Gingras, Alexandra Kindrat, Anne Mathiot, Inga Murawski,
Lenka Schorova

AGENDA

- 8:15 Registration (RI-MUHC Atrium)
- 8:45 Welcome remarks
- 9:00 Oral presentations: Session 1
- 10:35 Health Break and Open Poster Viewing
- 10:50 Poster Presentations (Groups 1-8)
- 12:00 Lunch and Open Poster Viewing
- 12:45 Oral presentations: Session 2
- 14:20 Health Break and Open Poster Viewing
- 14:35 Poster Presentations (Groups 9-17)
- 15:45 Closing remarks

ORAL PRESENTATIONS

Drs. Sylvia & Richard Cruess Amphitheatre - 1001 boul. Décarie, Montréal, QC, Block E

Session 1 - 9:00-10:35

- 1 Polymer-stabilized Liposomes for Enhanced Delivery of Cancer Immunotherapy Drug Combinations**
Presented by Adam Mouncef (Dr. Danuta Radzioch – IDIGH)
- 2 Predictors of 30- day Unplanned Healthcare Utilization Following Colorectal Surgery**
Presented by Emma Levine (Dr. Julio Flavio Fiore Jr. – SIS)
- 3 Defining the roles of CREB in maintaining sensory functions of AgRP neurons**
Presented by Nandini Gupta (Dr. Paul Sabatini – MeDiC)
- 4 The role of IFN- γ in imprinting alveolar macrophage functions**
Presented by Susan Cai (Dr. Maziar Divangahi – RESP)
- 5 Family-level Risk and Protective Factors for Early Child Development Across the African Continent: A Literature Review**
Presented by Zia Janmohamed (Dr. Marilyn Ahun – CHHD)
- 6 The Optimization of Single-Cell Suspensions Through the Digestion of the Carotid Atherosclerotic Plaque**
Presented by Rachel Aladeeb (Dr. Stella S. Daskalopoulou – CHAL)
- 7 Effect of psilocybin in anxiety and depressive-like behaviors induced by neuropathic pain**
Presented by Mariana Oliveira (Dr. Gabriella Gobbi – BRaIN)
- 8 Machine Learning Prediction of Hospital Admission of Elderly Cancer Patients Presenting in the Emergency Department**
Presented by Sepehr Babapour (Dr. James Tsui – CRP)

Session 2 - 12:45-14:20

- 9 Association Between Race/Ethnicity and Disease Phenotype in Systemic Sclerosis**
Presented by Camille Guertin (Dre Sabrina Hoa & Dre Sasha Bernatsky – IDIGH)
- 10 Evaluating the impact of “immune oncogenes” on Radiation Therapy response in muscle invasive bladder cancer.**
Presented by Orlando Yuan (Dr. Wassim Kassouf – CRP)
- 11 Sex Differences in the Association Between Social Determinants of Health and Adverse Outcomes for Atrial Fibrillation Patients: A UK Biobank Study**
Presented by Theodore Butskhrikidze (Dr. Louise Pilote – CHAL)
- 12 The Canadian Diabetes Prevention Program: Lessons from the NHS for a Healthier Future**
Presented by Samantha Jacobson (Dr. Kaberi Dasgupta – MeDiC)
- 13 Development of a Digital Biomarker of Motor Competency using Ankle Angular Velocity During a Vertical Jump: Proof of Concept in Healthy and Neurologically Impaired Adults**
Presented by Alessandra Granata (Dr. Nancy Mayo – BRaIN)
- 14 Feasibility of 3D-Echocardiography for LV and LA performance and dimensions in the immediate postnatal neonatal period - a prospective study**
Presented by Sariya Sahussarungsi (Dr. Gabriel Altit – CHHD)
- 15 Priming and Differentiating Adipose-derived Stem Cells Towards Ligamentogenic Lineage Under Near-Physiological Oxygen Tensions for Tissue Engineering Applications**
Presented by Sharmin Zahin (Dr. Rahul Gawri – SIS)
- 16 Estimated costs of tuberculosis-related activities and interventions in Brazil, 2023**
Presented by Elias Jabbour (Dr. Jonathon Campbell – RESP)

ABSTRACTS

ORAL PRESENTATIONS

1 - Polymer-stabilized Liposomes for Enhanced Delivery of Cancer Immunotherapy Drug Combinations

Adam Mouncef^{1, 2}, Radu Alexandru Paun^{2, 3}, Ling Li³, Thusanth Thuraisingam¹, Maryam Tabrizian^{3, 4}, Danuta Radzioch^{1, 2, 5}

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Introduction: Immune checkpoint inhibitors (ICI) such as ipilimumab and nivolumab have been recently approved for clinical use, demonstrating notable survival benefits for patients with late-stage cancers like advanced metastatic melanoma. Despite these advancements, not all patients respond effectively to ICI therapy, namely because of resistance to immune-mediated clearance in cancer cells and due to a lack of tumor immune infiltrates. Tumors that are resistant to ICI therapy typically exhibit aberrant cytokine signaling resulting in impaired immune activity. Compounds like 6-bromoindirubin-3'-oxime (BIO) and copper diethyldithiocarbamate (CuET) exhibit anti-neoplastic activities by interfering with GSK3 signaling and inducing endoplasmic reticulum (ER) stress, respectively, which can lead to cancer cell death. This drug combination is a promising candidate for enhancing the immune response in immunologically cold tumors. However, the hydrophobic nature of BIO and CuET has impeded the development of a stable and injectable nanoparticle formulation suitable for in vivo use.

Methods: The synthesis of the liposome-polymer nanoparticles encapsulating BIO and CuET (LPBC) was done using the solvent injection method. The nanoparticles were physicochemically characterized using standard transmission electron microscopy. Cytotoxicity assays were performed on multiple melanoma cell lines with established protocols. In vivo safety and efficacy of the formulation were assessed using syngeneic mouse models of melanoma.

Results: The synthesis process produced stable nanoparticles with the inclusion of polyvinylpyrrolidone as a stabilizing excipient. Transmission electron microscopy revealed that the nanoparticles ranged in diameter from 40 to 80 nm, demonstrating excellent stability and achieving over 90% encapsulation efficiency of both drugs. In ectopic melanoma mouse models harboring human driver mutations (YUMM1.7), the formulation reduced tumor growth and enhanced mouse survival. Additionally, in a metastatic melanoma mouse model (B16F10), LPBC substantially decreased tumor burden compared to the standard of care ICI therapy (α PD1 and α CTLA4).

Conclusions: The solvent injection method successfully produced a stable nanoparticle formulation of BIO and CuET. This novel formulation demonstrated potent activity in syngeneic melanoma mouse models resistant to current therapies and shows promise for enhancing the efficacy of cancer immunotherapy.

Source of funding: The authors thank CIHR, NSERC, FRQ and Faculty of Medicine and Health Sciences, McGill University (Summer Bursary to AM) for the financial support in the project.

2 - Predictors of 30- day Unplanned Healthcare Utilization Following Colorectal Surgery

Emma Levine BSc¹, Francesca Fermi MD^{1,2,3}, MD^{1,2,3}, Samin Shirzadi MD, MPH^{1,3} Julio F. Fiore Jr PhD^{1,2,3}

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Background: Unplanned healthcare utilization (i.e., emergency department [ED] visits and hospital readmissions) increases healthcare costs and patient dissatisfaction after colorectal surgery. Determining modifiable factors associated with unplanned healthcare utilization may inform strategies to improve perioperative care. The aim of this study is to identify predictors of 30-day unplanned healthcare utilization following colorectal surgery.

Methods: This cohort study included adult patients (≥ 18 yo) who underwent elective colorectal resection at two university-affiliated hospitals in Montreal, Canada. Preoperatively, patients completed questionnaires focused on their health status (i.e., physical function, mental health, catastrophizing). Demographic, surgical, and in-patient characteristics were obtained from the electronic medical records. Information on 30-day unplanned healthcare reutilization (composite outcome including ED visits and hospital readmissions) was obtained from medical records and a self-reported questionnaire. Logistic regression with stepwise backward selection and multiple imputations of missing data was used to identify significant predictors of unplanned healthcare utilization.

Results: A total of 333 patients were included (59 ± 15 years, 54% male, 64% laparoscopic, 31% rectal resection). The median length of stay (LOS) was 3 days [IQR 1-5] and the rate of 30-day unplanned healthcare utilization was 23% (21% ED visit and 10% readmission). On regression analysis, shorter LOS (OR 0.872 [CI 95% 0.799% - 0.950%]), 30-day complications (OR 19.51 [95% CI 9.274-41.04]), and higher pain catastrophizing (OR 1.030 [95% CI 1.002% - 1.059%]) were predictors of unplanned healthcare utilization.

Conclusions: This study supports that patients with shorter length of stay and postoperative complications are key targets for quality improvement initiatives to optimize healthcare utilization following colorectal surgery. Importantly, reducing pain catastrophizing (i.e., via pain education and expectation setting) has the potential to decrease healthcare utilization postoperatively.

Source of Funding: There is no source of funding for this study.

3 - Defining the roles of CREB in maintaining sensory functions of AgRP neurons

Nandini Gupta¹, Pierce Katz¹, João Alfredo Bolivar Pedroso¹, Paul Sabatini¹

¹MeDiC, RI-MUHC

Introduction: Obesity is one of the most significant health challenges being faced by about one in four adults and one in ten children in Canada. Obesity is defined as an excessive accumulation of excess body fat that arises as a result of an imbalance between energy intake and energy expenditure. This increase levels of leptin and insulin, leading to a resistant state to these two metabolically important hormones. This in turn increases the risk of developing cardiovascular diseases, type 2 diabetes, hypertension and cancer.

Within the central nervous system, the hypothalamus is responsible for regulating energy intake and expenditure. While the hypothalamus is made up of many cell types, a specific set of cells known as Agouti-Related Protein (AgRP) neurons found in the arcuate nucleus (ARC) are one of the most important for regulating energy balance. AgRP neurons balance internal energy signals with external factors, including the adipokine leptin and in response regulate both energy expenditure and appetite. Leptin is a critical regulator of energy balance, and its deficiency leads to excessive eating and obesity.

Cyclic AMP (cAMP) response element-binding protein (CREB) has been identified previously as a protein of interest in AgRP neurons. We hypothesize that early stages of energy surplus reduce CREB function, leading to weight gain and obesity. We also hypothesize that loss of CREB in AgRP neurons reduces responsiveness to leptin, and that increasing CREB activity will protect against diet induced obesity.

Material and methods: To determine the activity of CREB in AgRP neurons, immunofluorescent staining was performed for *c-fos* expression, which is a validated CREB target gene and serves as a proxy for CREB activity. C57Bl6 mice were kept on standard diet (SD), and high-fat diet (HFD) for 1 week or 8 weeks, and were either fasted or fed before euthanasia and tissue collection. This was done to study how energy surplus and deficiency affect transcription of CREB, and to determine when CREB dysfunctions during obesity.

Results: The number of cells expressing *c-fos* in the AgRP neurons were counted for mice under each feeding condition. In mice fed a standard diet and fasted for 16 hours had a high number of *c-fos* expressing cells in the arcuate nucleus compared to mice euthanized and perfused under *ad libitum* access to food. In contrast, there were no significant differences in FOS+ cells between the fasted and ad lib groups of both 1 and 8 weeks HFD mice. It was also observed that *c-fos* expression significantly reduces after only 1 week of diet induced obesity.

Conclusions: A high number of FOS+ cells in mice that were on standard diet and fasted suggests that CREB transcriptional activity is elevated under fasting conditions. However, low FOS+ cells in HFD conditions suggest that an energy surplus reduces CREB function. Since a dysfunction in CREB is seen after early stages of energy surplus (1-week HFD), this suggests that CREB could play a key role in driving obesity.

4 - The role of IFN- γ in imprinting alveolar macrophage functions

Susan Cai¹, Maziar Divangahi¹

¹McGill University

Background: As a part of the forefront line of defence in the lungs, alveolar macrophages (AMs) play a critical role in initiating, supporting and resolving pulmonary immune responses. Although it is generally accepted that interferon-gamma (IFN- γ) signalling will induce a 'pro-inflammatory' macrophage phenotype, the exact effects of IFN- γ on AMs remain unclear. As such, this project aims to characterize the impact of varying levels of IFN- γ exposure on AM function. It is hypothesized that sustained IFN- γ signalling may re-program AMs to better attenuate influenza A virus (IAV) infections.

Methods: Transgenic mice that constitutively produce low levels of IFN- γ (IFN- γ ARE del. mice) and C57BL/6 mice treated with intranasal injections of recombinant IFN- γ (rIFN- γ) are subjected to bronchoalveolar lavages (BALs) to recuperate AMs that have been exposed to prolonged IFN- γ signalling. AMs are then cultured and infected with IAV *in vitro*. Alterations to their ability to attenuate viral proliferation are assessed using plaque assays. Phenotypic, transcriptional and behavioural changes in these cells are analyzed via flow cytometry, reverse-transcriptase quantitative polymerase chain reaction (RT-qPCR), and metabolic assays, respectively.

Results: Flow cytometry analysis revealed that, under homeostatic conditions, heterozygous (+/-) IFN- γ ARE del. mice possess smaller AM populations when compared to wild-type C57BL/6 (WT) mice. However, a greater percentage of the AMs in these (+/-) IFN- γ ARE del. mice positively express MHC-II. Further analyses using the measured mean fluorescent intensities also indicate that these AMs may possess moderately enhanced CD80 expression. Thus, taking into consideration the extant knowledge on the general immunological effects of prolonged IFN- γ exposure, it is thought that the sustained IFN- γ signalling in these mice may induce a greater rate of AM death while concurrently impairing population replenishment via monocyte-derived macrophages. However, the observed enhancement of MHC-II and CD80 expression implies that chronic IFN- γ exposure will still induce phenotypic changes to support a type 1 immune response where AMs may be poised to activate and educate naive T cells.

Additionally, RT-qPCR showed a significant reduction in the expression of the viral IAV protein, NS1, 24 hours post-infection in the AMs collected from mice that had been treated with two injections of rIFN- γ (as compared to a negative control group and mice that had received only one injection). Metabolic analysis of these AMs also revealed elevated rates of glycolysis at baseline (under homeostatic conditions) and post-IAV infection. Similar changes in metabolism were observed with infected AMs recuperated from (+/-) IFN- γ ARE del. mice.

Conclusions: Collectively, these findings suggest that sustained exposure to IFN- γ may elicit phenotypic, transcriptional and metabolic changes in AMs to support functional re-programming that allows for improved attenuation of viral proliferation. Considering that our group has demonstrated that BCG vaccination will induce the expansion of a unique population of CX3CR1^{hi}, IFN- γ producing T cells that will prime AMs to clear IAV infection with improved efficiency, understanding the molecular details of how this protective re-programming is earned is critical in further clarifying our understanding of trained immunity.

Sources of funding: This project is supported by the Canadian Institutes of Health Research.

5 - Family-level Risk and Protective Factors for Early Child Development Across the African Continent: A Literature Review

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Background: Early childhood is a critical period that lays the foundation for children's lifelong health, wellbeing and achievement. 250 million children under the age of five in low- and middle-income countries (LMICs) are at risk of not realizing their developmental potential due to risk factors such as poverty, which increases children's risk of exposure to adversities including family stress and violence. Maternal depression is also associated with reduced parenting quality, which can have negative impacts on child development. Poor early child development has important societal implications including the maintenance of global inequalities and reduced economic productivity. Thus, identifying factors that contribute to positive developmental outcomes in young children is crucial. Although there is ample literature investigating biological factors that affect early child development, there is limited literature on psychosocial factors, especially in LMICs in Africa. This literature review aims to investigate the status of cognitive, language and socioemotional development of children (0-5 years) living in Africa and identify associated family-level risk and protective factors.

Methods: In an ongoing review that began June 26, 2024, we searched the following databases: Web of Science, PsycINFO, MEDLINE and Global Health Library. Studies were included if the population comprised children ages five and under, without underlying medical conditions, living in an African country and examined associations of family-level risk and protective factors with child cognitive, language, and socioemotional development. Articles were screened in *Covidence*. Thus far the electronic search has identified 378 articles including randomized controlled trials, scoping reviews, systematic reviews and meta-analyses. Three duplicates were removed and the remaining 375 articles underwent title and abstract screening, 309 of which were excluded. To date, the full text of 40 out of 66 articles have been assessed. Of these 40 articles, 13 were included in the review.

Results: The thirteen studies were conducted in South Africa (n=8), Ghana (n=2), Ethiopia (n=1), Tanzania (n=1) and the Democratic Republic of the Congo (n=1) and consisted of n = 12,045 families with children ages 3 months to 5 years. Findings reveal that risk factors such as maternal and paternal positive attitudes towards wife-beating, lower family socio-economic status and maternal experience of emotional intimate partner violence, psychotic disorders, post-natal depression and exposure to early life stress were negatively associated with children's literacy, numeracy, cognitive, language, executive functioning and working memory outcomes. On the other hand, protective factors such as parental involvement in activities with children (e.g., reading, drawing, having children's books at home), child attendance at pre-school, playing with children, caregiver participation in a book-sharing intervention and higher household socioeconomic status were associated with increased likelihood of on-track literacy-numeracy, social-emotional and learning-cognitive development. Studies' subgroup analyses revealed that some associations with protective factors were only present or were stronger for children living in rural areas.

Conclusions: Various psychosocial factors in the early childhood environment influence children's development. As the majority of studies present correlational findings, further longitudinal and experimental research is needed to determine causal associations between family-level risk and protective factors for early child development in African populations.

6 - The Optimization of Single-Cell Suspensions Through the Digestion of the Carotid Atherosclerotic Plaque

Rachel Aladeeb¹, Jae Hyun Byun¹, Helena Papacostas Quintanilla¹, Stella S. Daskalopoulou¹

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Background: Cardiovascular disease (CVD) remains the leading cause of death worldwide. Atherosclerosis is crucial in CVD, especially in the carotid arteries, where increased plaque instability is a major etiological factor causing ischemic strokes. These plaques contain various cell types, including fibroblasts, immune cells, endothelial cells, and smooth muscle cells; each contributing differently to the pathogenesis of atherosclerosis. Recent advancements in single-cell RNA sequencing (scRNA-seq) have provided a powerful alternative to bulk RNA sequencing, allowing for detailed transcriptional profiling at the single-cell level and the identification of complex and rare cell populations. However, low cell yield and viability following atherosclerotic plaque tissue digestion has limited the application of scRNA-seq. This research aims to optimize a protocol for generating high-quality single-cell suspensions from carotid atherosclerotic plaques, facilitating more precise and detailed scRNA-seq analysis.

Methods: Carotid plaque specimens were collected and analyzed from recruited patients (n=10) who underwent carotid endarterectomy at McGill University-affiliated hospitals. The plaque tissue was minced into small pieces and subjected to enzymatic digestion at 37°C for 3 hours. For the first 9 patients, the enzymatic cocktail included 5 mg/mL Collagenase I, III, and IV, 2 mg/mL Dispase, 0.6 mg/mL Elastase, 0.3 mg/mL DNase, and 0.3 mg/mL Hyaluronidase. This combination caused over-digestion, resulting in cell damage and reduced viability. For the 10th patient, optimization of the protocol consisted of removing Collagenase I and II, Dispase II, and Hyaluronidase to preserve cell integrity by reducing the harshness of the digestion process. The revised cocktail comprised 25 mg of Collagenase II (200 IU/mg), 5 mg/mL Collagenase IV, 4.5 mg of Soybean Trypsin Inhibitor, 0.6 mg/mL Elastase, and 0.2 mg/mL DNase. Following the enzymatic digestion, both protocols proceeded identically: the tissue was pipette-mixed, resuspended, and strained, followed by red blood cell lysis and centrifugation to remove cell debris. Cell capture and scRNA-seq analysis were then conducted to assess cell yield and viability.

Results: The optimized protocol resulted in a significant increase in cell yield and viability as assessed via fluorescence and downstream scRNA-seq. 10,000 to 15,000 viable cells were obtained with the optimized protocol, compared to <300 viable cells with the initial protocol. Key optimizations included removing Collagenase I and III, Dispase II, and Hyaluronidase from the enzyme mix and adding 25mg of Collagenase II [200IU/mg] and 4.5mg Soybean Trypsin Inhibitor.

Conclusions: The optimization of the single-cell suspension protocol for carotid atherosclerotic plaques resulted in a significant increase in cell yield and viability, which is essential for detailed transcriptional profiling using scRNA-seq. Future research should focus on further validating the protocol across larger sample sizes and exploring additional optimization parameters. The application of this protocol to other types of atherosclerotic plaques could also provide broader insights into cardiovascular disease mechanisms.

Source of funding: This study was funded by the Canadian Institutes for Health Research (Projects: 192142, 148966, 145589).

7 - Effect of psilocybin in anxiety and depressive-like behaviors induced by neuropathic pain

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Introduction: Neuropathic pain (NP) is a chronic pain disorder that manifests through neurochemical changes in the central and peripheral nervous system. NP has been correlated to anxiety and depressive symptoms in patients (Moriarty et al., 2017; Povedano et al., 2007). Psychedelic drugs, particularly psilocybin, have received increasing attention in recent years for the treatment of depression, end-of-life anxiety, and neuropsychiatry disorders. For this, our objective is to assess the potential analgesic, anxiolytic, and anhedonic effects of psilocybin in anxiety and depressive-like behaviors induced by neuropathic pain in rats.

Material and Methods: Male Sprague Dawley rats (n=20), weighing 130g to 150g at the beginning of the experiment were used. Induction of NP was made by Spinal Nerve Ligation L5-L6 (SNL, Kim and Chung, 1992) and SHAM-operated animals were used as a control. 15 days after surgery, the mechanical withdrawal threshold was measured using Von Frey filaments. Animals that show signs of severe locomotion impairments were discarded. Rats were randomly assigned to four groups: I - L5-L6 psilocybin (3 mg/kg i.p. n = 5); II - L5-L6 Vehicle (Saline solution 0.9%, n =5); III - SHAM psilocyn (3 mg/kg i.p. n=5); IV - SHAM Vehicle (n =4). For acute administration, mechanical allodynia was assessed using Von Frey filaments at time 0 (baseline), 30, 60, 90, 120, 180, 240 and 300 min post-treatment. In different animals, Open field Test (OFT) and Elevated Plus Maze (EPM) were performed 20 min after treatment administration. For repeated administration, all animals will receive vehicle (saline 0.9% i.p.) or psilocybin (3 mg/kg i.p.) for 7 days, and allodynia, OFT, and EPM were made on day 8 (24h after last administration).

Results: Two Way ANOVA with RM analysis after acute administration of psilocybin (3 mg/kg) in mechanical allodynia shows a difference by treatment ($F_{(3,17)}=6.96$, $P=0.002$), time ($F_{(2.84, 48.36)}=3.47$, $P=0.02$) and interaction ($F_{(18, 102)}=1.805$, $P=0.03$), showing a possible analgesic effect of psilocybin in NP animals. One-way ANOVA for the OFT shows no significant difference in the distance traveled ($F_{(3,8)}=0.52$, $P=0.67$) and anxiety-like behavior ($F_{(3,8)}=0.09$, $P=0.96$). Similarly, In the EPM, ANOVA indicates no difference between groups ($F_{(3,6)}=1.68$, $P=0.26$). However, a trend is observed since NP animals treated with psilocybin increase the number of entrances to the open arm (mean=4) in comparison with NP animals not treated (mean=0). For repeated administration, 7 days of psilocybin does not change the mechanical threshold in NP animals or sham ($p>0.05$).

Conclusion: Acute administration of psilocybin exerts an analgesic effect and shows a trend of anxiolytic effect in NP animals. Due to the lower number of animals, no statistical differences were found, for this more experiments need to be done.

Sources of Funding: CAPES-PrInt

8 - Machine Learning Prediction of Hospital Admission of Elderly Cancer Patients Presenting in the Emergency Department

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Background: The current emergency department (ED) overcrowding poses significant risks for elderly cancer patients. This study explores the use of Machine Learning (ML) to predict hospital admissions to expedite interventions and hospitalization.

Methods: ED visit data from January 1, 2014, to December 31, 2023 was collected. Cancer patients aged 75 and above were included. Serial vital signs (VS), along with their timestamps, were extracted. Implausible blood pressure (BP) measurements and visits with single vital sign readings were discarded. The training/validation and test datasets were split using a 90:10 ratio. A 5-fold cross-validation technique was employed.

First, to predict if a patient would be admitted, the data was divided into four-hour intervals, with various aggregates of vital signs data, as well as the number of physician hand-overs, consultation requests, and investigations used as inputs. Three Recurrent Neural Networks (RNN) were used (classic RNN (cRNN), the Long Short Term Memory (LSTM), and the Gate Recurrent Unit (GRU)) and their performance was evaluated on the test set.

Second, given that BP is recorded at variable intervals, we aimed to generate a new set of features by creating BP embeddings to capture underlying relationships. Serial BP measurements with corresponding timestamps served as input, while the last recorded BP, and mean arterial pressure (MAP) served as the prediction targets. A GRU model was trained, and its performance was evaluated using Mean Squared Error (MSE), then compared with three baseline models where the target was set to (1) the second to last BP, (2) the average of prior serial BPs, and (3) the second to last BP with added standard Gaussian noise. ANOVA and post-hoc Tukey HSD tests were used to analyze the differences between group means. K-means clustering on the GRU embeddings identified clusters, considering the Elbow method and Silhouette score.

Results: A total of 14,569 ED visits were obtained. For the hospital admission prediction task, 13,177 visits remained after exclusions, with 45.85% of visits leading to an admission. Among the cRNN, LSTM, and GRU models, the latter achieved the highest performance: accuracy (76.6%), F1-score (76.6%), and AUC-ROC (0.853). For the BP embedding generation task, 109,227 BP measurements across 11,559 visits were analyzed, after exclusions of abnormal values. The MSE for baseline models (1), (2), and (3) were 0.9, 0.696, and 0.906, respectively, compared with the GRU's MSE of 0.557. ANOVA showed an f-score with a p-value < 0.001. Post-hoc Tukey HSD indicated the GRU's MSE was significantly smaller than the other models. Cluster analysis (k=3) showed BP measurements in Cluster A often exhibited low BP, while Cluster C exhibited high BP.

Conclusion: First, we demonstrated promising performance with the GRU model to predict admissions in elderly cancer patients presenting to the ED. Second, we showed that meaningful embeddings can be created from serial BP measurements of varying intervals. future work will explore the use of BP embeddings to enhance model accuracy and robustness as well as explore further feature engineering.

Source of funding: MUHC Foundation.

9 - Association Between Race/Ethnicity and Disease Phenotype in Systemic Sclerosis

Camille Guertin^{1, 2, 3, 4}, Sasha Bernatsky^{1, 2}, Sabrina Hoa^{3, 4}

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Background: Systemic sclerosis (SSc) is an autoimmune disease resulting in vasculopathy, inflammation and fibrosis. Studies mostly done in the United States and in Europe have reported ethnic disparities in SSc phenotypes. This study examines the association between ethnicity and SSc phenotype in Canadian patients.

Methods: Retrospective multicentric study using prospectively-collected data from the Canadian Scleroderma Research Group (CSRG) cohort. Patients over 18 years of age with a diagnosis of SSc were recruited and data were collected annually using standardized questionnaires. Ethnicity was self-reported by patients. Descriptive statistics, t-tests, Mann-Whitney U, chi-square and Fisher's exact tests were used to compare the demographic, clinical and serological characteristics of patients according to ethnicity group.

Results: Of the 1727 patients in the CSRG, 80% identified as White (n=1385), 4.6 % as Indigenous (n=79), 3% as Latin American (n=58), 1.6% as Middle Eastern (n=27), 1.5% as East/Southeast Asian (n=26), 1.2 % as Black (n=21) and 0.8 % as South Asian (n=13). White patients were generally older at cohort inception compared to other ethnicities (56.4 vs 49.6 years, $p < 0.001$). SSc affected mostly women, but men were affected in higher proportions among South Asian (39%) and East/Southeast Asian (23%) patients compared to other ethnicities (28% vs 13%, $p = 0.024$). Although Raynaud's phenomenon is almost universal in SSc, its prevalence was lower among East/Southeast Asian patients (86% vs 97%, $p = 0.002$), who also had numerically lower frequency of digital ulcers compared to other ethnicities (32% vs 47%, $p = 0.302$). Arthritis was highly prevalent among Latin American (55%), Black (60%) and Indigenous (54%) patients. Indigenous patients had the highest prevalence of lower gastrointestinal involvement, including malabsorption (22% vs 9%, $p = 0.002$), bacterial overgrowth (15% vs 6%, $p = 0.032$), pseudo-obstruction (7% vs 3%, $p = 0.210$) and the need for hyperalimentation (9% vs 2%, $p = 0.003$). White patients had the highest frequency of limited SSc (62% vs 48%, $p = 0.001$) and pulmonary arterial hypertension (14% vs 11%, $p = 0.621$), whereas Black patients had the highest frequency of diffuse SSc (67% vs 34%, $p = 0.016$), telangiectasias (79% vs 26%, $p < 0.001$), myositis (38% vs 9%, $p < 0.001$) and interstitial lung disease (47% vs 30%, $p = 0.296$), with the lowest pulmonary function test values (mean FVC 74.9 vs 92.5, $p = 0.003$; mean TLC 76.5 vs 94.3 $p = 0.001$; DLCO: 57.2 vs 70.5, $p = 0.041$). Anticentromere autoantibodies (ACA) were present in about one third of SSc patients, but were rare among Black patients (6%) vs 36%, $p = 0.030$). Conversely, antitopoisomerase I autoantibodies (ATA) were present in about one third of Latin American, Black, East/Southeast Asian, Middle Eastern and South Asian patients, but in only 13% of White and Indigenous patients. Anti-RNA polymerase III autoantibodies were overrepresented among Indigenous patients (30% vs 16%, $p = 0.01$).

Conclusion: In this Canadian cohort, ethnicity was associated with distinct SSc phenotypes. This study can help improve patient care and reduce health disparities by informing clinicians and patients on targeted screening and treatment strategies according to patient ethnicity.

Source of funding: Canadian Rheumatology Association Foundation

10 - Evaluating the impact of “immune oncogenes” on Radiation Therapy response in muscle invasive bladder cancer.

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Introduction: Muscle Invasive Bladder Cancer (MIBC) is a type of bladder cancer that requires prompt treatment due to its high rate of mortality. Depending on the severity of the tumour, patients head directly to radical cystectomy, which is the complete removal of the bladder. Unfortunately, this significantly affects the quality of life and has a 5-year survival rate of only 50%. Radiation therapy (RT) is an attractive bladder-preservation option. However, the efficacy of RT needs improvement since 30% of patients do not respond and will require surgery, and half will develop metastasis. Emerging evidence suggests RT drives additional immunomodulatory effects beyond its direct DNA damage cytotoxic impact on cancer cells. Therefore, identification of immunological biomarkers that can help predict patients' responses to RT is crucial to the personalization of bladder preservation management of MIBC.

Material and Methods: Gene expression from 150 Formalin-Fixed Paraffin-Embedded tumor biopsies pre-radiation therapy were obtained using the GeoMx®Whole Transcriptome Atlas (WTA) from NanoString. 185 immune response-related genes of interest were identified and studied. Data was retrieved from patient tumours where immune cells were abundant (PanCK-), or where tumour cells were abundant (PanCK+). Patient were separated into two groups depending on their response to RT: Complete Response (CR) and Non-Responsive (NR). Data analysis was performed with three different groupings. Group 1 consisted of all CR and NR patients and was compared based on PanCK- and PanCK+. Then, Group 2 contained only PanCK+ and Group 3 consisted of only PanCK- and were both compared on CR and NR. Principal Component Analysis (PCA), Heatmap, and Differential Gene Expression (DGE) using the programming language R were conducted to identify potential immunological biomarkers.

Results: Statistical analyses of Group 1 suggest variability between PanCK+ and PanCK- and upregulation in NR patients of COL3A1 gene, which contributes to structural changes favouring tumour growth and metastasis. In PanCK+, results suggest that IDO1, a gene modulating the immune response, and genes related to the HLA protein, which are associated with antigen presentation, are downregulated in NR patients. Finally, in PanCK-, the volcano plot from DGE indicates a downregulation of EBI3, a gene that plays a role in antitumor T-cell responses, and an upregulation of COL3A1 and THBS1, which in high expression is correlated with bladder cancer growth.

Conclusion: The results of this study shed light on some potential immunological biomarkers for MIBC. If confirmed from further evaluation, these genes could help predict RT response and identify patients who will benefit from bladder preservation therapy.

Source of Funding: This study was supported by the Cancer Institute of Health Research (CIHR).

11 - Sex Differences in the Association Between Social Determinants of Health and Adverse Outcomes for Atrial Fibrillation Patients: A UK Biobank Study

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Background: Atrial fibrillation (AF) is a cardiac arrhythmia affecting millions of people worldwide. AF is associated with significantly increased morbidity and adverse clinical outcomes, including a fivefold increased risk of stroke and an all-cause mortality rate of up to 10% within 1 year. A systematic review has demonstrated the limited predictive ability of many currently used risk prediction scores, possibly due to their exclusion of social determinants of health (SDOH) variables.

Objective: The objective was to identify and assess sex-specific differences in SDOH variables that are associated with adverse cardiovascular events in patients with AF using data from the UK Biobank (UKBB).

Methods: The UKBB is a prospective cohort study with over 500,000 participants, aged 40 to 69 years old, enrolled between 2006 and 2010. The outcome was a composite of major adverse cardiovascular events (MACE) and all-cause mortality (MACEM). We included patients who were diagnosed with AF at the time of enrolment based on their ICD-10 classification. We excluded participants with a history of MACE prior to AF diagnosis, participants with a history of MACE prior to UKBB enrollment, and participants with AF onset after enrollment. SDOH variables were selected based on combined consideration of clinical relevance, social and gender-related factors, and information available within the UKBB dataset. In males and females separately, Cox proportional hazards models were used to test the association between various identified SDOH and the outcome, adjusted for anticoagulation/antithrombotic medication usage, BMI, time from AF onset to enrollment, and CHA2DS2-VASc variables, which include age, sex, and clinical variables such as congestive heart failure, hypertension, diabetes mellitus, vascular disease, and previous history of stroke, transient ischemic attack, or thrombo-embolism.

Results: We selected 6,262 participants (31.5% females) with AF. The mean age was 62.58 ± 6.07 . We found sex differences in the association between various identified SDOH and the risk of MACEM in patients with AF. Among them, emotional distress (Female HR: 1.08, 95% CI=0.84-1.40; Male HR: 1.17, 95% CI=1.01-1.36) and material deprivation (Female HR: 1.00, 95% CI=0.75-1.35; Male HR: 1.23, 95% CI=1.03-1.47) were statistically significant in males, but not in females, being associated with a higher risk of MACEM in males with AF. Additionally, being unemployed (Female HR: 1.64, 95% CI=1.10-2.45; Male HR: 1.28, 95% CI=1.05-1.56) and smoking (Female HR: 2.41, 95% CI=1.59-3.63; Male HR: 1.72, 95% CI=1.36-2.18) were statistically significantly associated with a higher risk of MACEM in both males and females with AF.

Conclusion: We found sex differences in the association of certain SDOH and increased MACEM risk in AF patients. Our findings highlight the need to stratify risk prediction models between males and females given the variability of the impact of various SDOH on risk outcomes.

Source of Funding: Funding for this study was obtained from the Canadian Institutes of Health Research (PJT-178237).

12 - The Canadian Diabetes Prevention Program: Lessons from the NHS for a Healthier Future

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Background Type 2 diabetes (T2D) has emerged as a significant public health issue over the past two decades, driven by obesogenic environments that have led to increased prevalence of excess weight and reduced physical activity. This epidemic has placed substantial strain on the healthcare system and economy, leading to numerous health complications. Diabetes Canada developed the Diabetes 360° Strategy to address this crisis, resulting in the passage of Bill C-237 in 2021, to build a national framework for diabetes prevention and treatment (1). In tandem with this process, we seek to examine the successful implementation of a publicly-funded national diabetes prevention program in England, and consider how this model could be tailored to Canadian provinces.

Methods We are reviewing published literature and reports from the National Health Service (NHS) in England to delineate the steps involved in building, implementing, and monitoring the program. We will consider each of these in relationship to structures, assets, and barriers in Quebec, to ascertain if the NHS model could be executed in our province. A comprehensive review of the NHS DPP's development and implementation process was conducted, including the systematic review of evidence, needs assessment, cost analysis, and securing of funding and political support. Data from international trials and evidence-based practices involving dietary changes, physical activity, and behavior change techniques were analyzed.

Results: The first steps of the NHS Diabetes Prevention Program development included a systematic review of the evidence, a needs assessment, and cost analysis. This evidence was used to secure funding from the Treasury Board. This was followed by a call to vendors to meet specifications to deliver DPP. The vendors must provide specific performance data at particular time points to receive continued funding. The program includes 13 in-person sessions (1 to 2 hours each) over 9 months, including individual and group-based activities. A digital version is now available, incorporating wearables for physical activity monitoring, health coach apps, and online peer support groups led by coaches (2). The goals are weight loss and adherence to dietary and physical activity guidelines (2). A cohort study using data from April 1, 2016 (NDPP introduction) to March 31, 2020 showed that the NHS DPP demonstrated a 20% reduction in type 2 diabetes incidence (3). By April 2020, the program had over half a million referrals (4).

Conclusion: The Diabetes 360° effort and lobbying by Diabetes Canada have set the stage for a comprehensive national strategy. By learning from the NHS DPP, we have to the potential to build an effective DPP in Canada.

13 - Development of a Digital Biomarker of Motor Competency using Ankle Angular Velocity During a Vertical Jump: Proof of Concept in Healthy and Neurologically Impaired Adults

Alessandra Granata¹, Natasha Hassija², Ezinne Ekediegwu², Eren Timurtas², Nancy Mayo²

¹Intern, M.Sc. (Applied) Biotechnology at McGill University, ²Centre for Outcomes Research and Education (CORE)

Introduction: Impairments in the neurological system invariably affect motor function. A common neurological condition is Parkinson's disease (PD) with characteristic effects on motor function that progress over time. Traditional tests of motor function often lack sensitivity to detect subtle motor changes creating a need for effective clinical markers to monitor disease progression and tailor therapies. This study explores whether recordings from a wearable sensor comprising inertial measurement units (IMUs) taken during performance of a vertical jump test has potential as a digital biomarker for PD progression. The hypothesis is that the ankle angular velocity during vertical jumps can provide quantifiable and sensitive measures of motor competency in PD patients, and the goal is to contribute evidence of this.

Materials and Methods: Our project uses the Heel2Toe sensor technology, developed by PhysioBiometrics Inc. This device includes a gyroscope that captures ankle angular velocity (AV) in degrees per second during a jump, providing precise data on jump dynamics. We first assessed 58 healthy students, aged 20-25 years, to establish typical jumping values. These values are then extrapolated to an older population using Statistics Canada data: "Normative-referenced percentile values for physical fitness among Canadians". The jumps of people with PD were also assessed, and their performance compared to the age and sex extrapolated values. The jump metrics assessed in all populations included: AV during all jump phases (push off, transition to flight, landing preparation, and landing), ankle wobble during flight, landing to push off AV ratio, and flight time (msec).

Results: Selected results from among the 20-25 age group showed that the average push-off speed was -462.5 deg/s (SD 130.0) with an average transition speed of 242.4 deg/s (SD 328.9) for men and lower for women, 106.8 deg/s (SD 120.0). The average landing speed was 972.0 deg/s (SD 344.7) yielding a landing-to-push-off ratio of 2.19 (SD 0.99). The average flight time was 64.9 msec for men (SD:12.7), and shorter for women, 55.0 msec (SD 8.3). Data from people with PD are being processed. The most consistent jump metric was flight time with a coefficient of variation (CV) of 19% for men and 15% for women. There was a high degree of variability (>30%) in push-off and landing AV (and their ratio) not explained by sex or height. Data for the older population and Parkinson's patients, as well as their comparison, are being processed.

Conclusions: Data from the young, healthy population showed considerable homogeneity for flight time likely explained by push-off metrics. These measurements have potential to create an algorithm for a digital biomarker for motor competency that could then be translated for use in people with PD and people with other conditions that affect the motor system.

Source of funding: This project was supported by a CIHR grant on active aging as well as funding from PhysioBiometrics Inc.

14 - Feasibility of 3D-Echocardiography for LV and LA performance and dimensions in the immediate postnatal neonatal period - a prospective study.

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Introduction: The neonatal population lacks substantial data on parameters derived from three-dimensional echocardiography (3D-ECHO) pertaining to left ventricular (LV) dimensions and function. Utilization of 3D-ECHO enables the acquisition of comprehensive cardiac volumes, encompassing all cardiac walls throughout the cardiac cycle. Employing speckle-tracking (STE) analysis, enables the reconstruction of cardiac volumes during contraction and filling phases. This innovative approach holds potential for discerning subtle alterations in cardiac performance attributable to various pathologies, thereby facilitating the identification of neonates at heightened cardiovascular risk.

Methods: Our principal aim was to assess the feasibility of acquiring 3-D echocardiography during the immediate postnatal neonatal period and to delineate parameters of cardiac function and dimension in healthy newborns within the initial 48 hours of life. Additionally, our secondary objectives included examining whether factors such as age at echocardiography (in hours), sex, or birth weight could exert an influence on these parameters. After consent, ECHO using the X2-matrix probe and Philips Epiq7 was performed by trained professionals. A blinded rater extracted off-line LV and LA parameters using Speckle-tracking ECHO (STE) with TomTEC Arena. Descriptive statistics and regressions were used to analyze the data.

Results: Out of 51 newborns enrolled, 3D-ECHO and STE for LV was feasible in 50 infants (98%). Of these 50, 54% (n=27) were male. They were term (mean gestational age of 39.4[1.0] weeks) with a birthweight of 3461±414 grams. ECHO was performed close to 24 hours of life. Markers of LV volumes and function were found to have no differences based on timing of ECHO (< or ≥24 hours) or sex. By linear regression, weight at echocardiography was associated to the LV end-diastolic volume (b=129, p=0.002) and LV length (b=68, p<0.001), but not to LV ejection fraction. This was observed by graphical trends. Birthweight was associated to cardiac longitudinal deformation (GLS: b=-27.6, p=0.01), a marker of LV contraction. Left atrial dimensions by 2D-echocardiography were also associated with weight. There were no discernible variances observed in markers of left ventricular (LV) volumes and function based on the timing of ECHO (< or ≥24 hours) or sex.

Conclusion: We demonstrated the feasibility of assessing LV dimensions and function of neonates using 3D-echocardiography, during their transitional period. We found an association between certain markers of LV and birthweight. **Future studies may use our 3D normative dataset to compare pathological conditions that may have subtle impact on early neonatal cardiac performance.**

Source of funding: The NeoCardioLab of Dr Gabriel Altit and its platforms were funded by the Department of Pediatrics of McGill University, the Just for Kids Foundation, the Division of Neonatology of McGill University, the Foundation of Stars, as well as the Grand Defi Pierre Lavoie.

15 - Priming and Differentiating Adipose-derived Stem Cells Towards Ligamentogenic Lineage Under Near-Physiological Oxygen Tensions for Tissue Engineering Applications

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¹SIS (Surgical and Interventional Sciences)

Background: Anterior cruciate ligament (ACL) rupture is one of the most prevalent knee injuries. Presently, ACL reconstruction surgeries using autografts or allografts suffer multiple drawbacks, including donor site morbidity, slow graft incorporation, high re-rupture rates, disease transmission, and increased cost. Artificial Ligaments designed through tissue engineering can potentially replace the use of autografts/allografts. Mesenchymal stem cells (MSCs) can be harvested from adipose tissue and differentiated into ligament tissue-forming cells. Yet, numerous challenges persist in successfully integrating ligament tissue-forming cells into the physiological environment of the human body. One primary hurdle to overcome is the sensitivity of these cells to nutrient and oxygen deprivation encountered upon implantation. Hypoxia decreases MSCs' survival and extracellular matrix production ability. One proposed strategy to overcome this challenge involves priming MSCs in a hypoxic environment and exposing them to growth factors to drive their ligamentogenic differentiation. Hence, this research project aims to examine the effects of culturing adipose-derived MSCs in a near-physiological hypoxic environment and supplementing them with TGF- β and bFGF on their ligamentogenic differentiation. In this study, we hypothesize that culturing MSCs in a near-physiological environment and using specific growth factors enhances their ligamentogenic differentiation for making bioengineered ligament tissue.

Methods: The human adipose-derived mesenchymal stem cells (hAD-MSCs) are cultured for 10 days at 37°C. The differentiation medium consists of DMEM supplemented with 10% Fetal Bovine Serum, 1% Antibiotic/Antimycotic, 5ng/mL TGF- β , and 1ng/ml bFGF. These cells are cultured under three different oxygen levels: atmospheric oxygen levels (20% O₂), intravenous oxygen tension (5% O₂), and intraarticular oxygen tension (2% O₂). For the atmospheric oxygen conditions, the culture plates are placed in a standard incubator with 5% CO₂ at 37°C. For intravenous and intraarticular oxygen tension, specialized incubator hypoxia chambers are sealed and flushed with 5% O₂ and 2% O₂, respectively, then placed inside an incubator at 37°C for the duration of the experiment. The differentiation medium is changed every third day. After the 10-day incubation period, cell viability is assessed using a trypan blue exclusion assay, metabolic activity are measured using AlamarBlue™ reagent, and the gene expression of various ligament markers (Collagen type 1, Collagen type 3, Scleraxis, and Tenascin-C) are analyzed using qPCR. All data sets undergo normality testing, and appropriate statistical analyses are performed using GraphPad Prism 10.

Results: Our data shows that adipose-derived MSCs have an increased proliferation rate when cultured in near physiological culture conditions. It is expected that adipose-derived MSCs show an enhanced ligamentogenic phenotype when primed and differentiated under near physiological culture conditions. Hence, we expect an upregulation of ligament marker expression in cells cultured under hypoxic conditions with TGF- β and bFGF compared to their counterparts grown in atmospheric oxygen tension. adipose-derived MSCs would show increased metabolic activity and proliferation when cultured in near physiological culture conditions.

Conclusions: Successful outcomes can advance bioengineered ligament implants, improve ACL rupture surgeries, and potentially enhance patients' quality of life.

Source of Funding: This project is funded by the Langevin-Danco Family Research Bursary in the Faculty of Medicine and Health Sciences.

16 - Estimated costs of tuberculosis-related activities and interventions in Brazil, 2023

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Introduction: While Brazil is a moderate tuberculosis incidence country, it is one of the 30 high TB burden countries globally given its population size. To reduce and ultimately eliminate tuberculosis, scaling up screening and prevention strategies will be essential. We estimated costs of tuberculosis-related activities to support the implementation of these strategies in Brazil.

Methods: We leveraged multiple databases and healthcare worker salaries from five different large cities in Brazil (Manaus, Recife, Porto Alegre, São Paulo, and Rio de Janeiro) to estimate costs of tuberculosis-related activities and their dispersion. We fit cost estimates to probabilistic distributions and estimated mean and 95% uncertainty ranges (95% UR) for specific activities, and combined activities according to national algorithms for tuberculosis diagnosis and treatment to estimate costs for different groups of activities in 2023 BRL and USD.

Results: After grouping activities together, we estimated the mean (95% UR) cost of testing children for TB infection with a tuberculin skin test or interferon-gamma release assay and providing three months of once-weekly isoniazid and rifapentine was USD\$47.43 (24.52-81.63) and USD\$66.49 (42.53-100.47), respectively. Shorter treatments (6 months vs. 18 months) for rifampin-resistant tuberculosis were much more inexpensive with a cost of USD\$3517.75 (1169.04-7329.54) for a 6-month regimen and USD\$7910.06 (2533.03-16,717.08) for an 18-month regimen in adults.

Conclusion: There are important cost differences in tuberculosis-related care depending on diagnostic and treatment choices. These data are essential to inform scale-up of tuberculosis screening and prevention activities in Brazil.

POSTER PRESENTATIONS

Elsbeth McConnell Atrium - 1001 boul. Décarie, Montréal, QC, Block E

MORNING SESSION – GROUPS 1-8

Group 1:

- 1 Investigating the Role of Nodal During Murine Pregnancy**
Presented by Chanel Gabriel (Dr. Daniel Dufort – CHHD)
- 2 Constructing a Plasmid to Model PFA Ependymomas in Mice Models**
Presented by Noa Bouzaglo (Dr. Sampath Loganathan – CRP)
- 3 Machine Learning Analysis of Arterial Stiffness Trends throughout Pregnancy to Predict the Development of Preterm, Term and Postpartum Preeclampsia**
Presented by Allison Engo (Dr. Stella S. Daskalopoulou – CHAL)
- 4 Development of a ChatGPT-Powered Crisis and Suicidal Ideation Management Module for an HIV Self-Management Chatbot**
Presented by Sebastian Villanueva (Dr. Bertrand Lebouché – IDIGH)
- 5 CT scan derived mean curvature of isophotes (MCI) for the detection of alpha-1 antitrypsin deficiency (AATD)- related emphysema**
Presented by Zlatitsa Todorova (Dr. Ronald J. Dandurand – RESP)
- 6 The Role of TNF in Synaptic Function from Neuron and Glia Culture Models**
Presented by Fedgi Dony Gaspard (Dr. David Stellwagen – BRaIN)

Group 2:

- 7 The Role of Innate Immune Cells in Colorectal Cancer Liver Metastases**
Presented by Benjamin Tordjman (Dr. Peter Metrakos – CRP)
- 8 Patient and service outcomes of administering an ePROM of barriers to adherence to antiretroviral therapy to people with HIV through a patient portal**
Presented by MHD Amir Chalati (Dr. Bertrand Lebouche – IDIGH)
- 9 Two-photon optogenetic mapping of connectivity in layer-6 pyramidal cells of mouse primary motor cortex**
Presented by Linn Dragsted (Dr. Per Jesper Sjöström – BRaIN)
- 10 The Toxicological Effect of Cannabis Smoke in Alveolar Macrophages**
Presented by Albert Huang (Dr. Carolyn Baglole – RESP)
- 11 Sex Differences in the Impact of Hypertension on the Heart, Brain, and Kidney: A Systematic Review**
Presented by Léa-Mai Simard (Dr. Louise Pilote – CHAL)
- 12 Diagnostic Potential of Spectral Oscillometry versus Spirometry in Asthma**
Presented by Dev Patel (Dr. Ron Dandurand – RESP)

Group 3:

- 13 The Impact of POLR3-related Leukodystrophy on Non-Affected Family Members: A Qualitative Study**
Presented by Kelly-Ann Thibault (Dr. Geneviève Bernard – CHHD)
- 14 Investigating Antimicrobial Activity of Bacterial Isolates from Canadian High Arctic Soil**
Presented by Maja Lambeck (Dr. Dao Nguyen – RESP)
- 15 The Dynamics of Suppression in Interocular Synchronicity in Human Vision**
Presented by Miriam Sharon Bucur (Dr. Alexandre Reynaud – BRaIN)
- 16 Circulating Lipid Profile Markers of Plaque Instability in Individuals with Severe Carotid Atherosclerosis**
Presented by Irem Engin (Dr. Stella S. Daskalopoulou – CHAL)
- 17 Value and Appropriateness of Inpatient ANA Testing: A Clinical Audit**
Presented by Megha Udupa (Dr. Arielle Mendel – IDIGH)
- 18 Synthetic Double-stranded RNA Induces M2-like, Anti-Inflammatory Macrophage Phenotypes In Vitro**
Presented by Seungmin (Daniel) Pyo (Dr. James G. Martin – RESP)

Group 4:

- 19 **Targeting O-GlcNAc Transferase with small molecule inhibitors in human leiomyosarcoma cell lines**
Presented by Sandip Das (Dr. Joanna Przybyl – CRP)
- 20 **Sex Differences in the Impact of Extreme Heat on Cardiovascular Disease Outcomes: A Systematic Review and Meta-Analysis**
Presented by Fahima Khan (Dr. Louise Pilote – CHAL)
- 21 **Proof-of-principal for the novel mRNA-based cure of rare genetic disease Cystinosis**
Presented by Alec Vong (Dr. Paul Goodyer – CHHD)
- 22 **Role of Caldesmon in Smooth Muscle Efficient Force Maintenance**
Presented by Sean Fletcher (Dr. Anne-Marie Lauzon - RESP)
- 23 **Reading Efficiency in Amblyopia**
Presented by Dasha Vanichkina (Dr. Alexandre Reynaud – BRaIN)
- 24 **A bioinformatics approach to investigate emerging variants of Chikungunya virus from the 2020 Cambodia epidemic**
Presented by Natalie Abuelsamen (Dr. Silvia Vidal – IDIGH)

Group 5:

- 25 **Dietary Risk Factors for Coronary Artery Disease: a UK Biobank Study**
Presented by Janel Lacey (Dr Jamie Engert -CHAL)
- 26 **Prevalence and Correlates of Mental Health Problems in Young (Birth-5 Years) Children across Africa: A Literature Review**
Presented by Josie Brooks (Dr. Marilyn Ahun – CHHD)
- 27 **Exploring FDA-Approved Drugs for Sensitizing Chemotherapy-Resistant Cancer Cells: Establishing Dose-Response Baselines for Methotrexate, Etoposide, and Topotecan**
Presented by Albert Choi (Dr. Lorenzo Ferri – CRP)
- 28 **Assessment of Optimal Inhaler Therapy Strategies in the Management of Acute Exacerbations of COPD (AECOPDs) using Oscillometry: A Cross-Sectional Study**
Presented by Alexandre Siou (Dr. Bryan Ross – RESP)
- 29 **Potential withdrawal effect of the 5-HT receptor agonist psilocybin in rats**
Presented by Vitor Bruno (Dr. Gabriella Gobbi – BRaIN)
- 30 **Investigating the Protein-Protein Interactions of Slit Diaphragm Protein Crb2**
Presented by Emily Foxman (Dr. Tomoko Takano – MeDiC)

Group 6:

- 31 **Overexpression of Zfh2 disturbs glial cell morphology in Drosophila**
Presented by Sam Kunesch (Dr. Don van Meyel – BRaIN)
- 32 **Evaluation of Psych Corps Ghana's Psychological First-Aid Training**
Presented by Chanelle Lawson-Lartego, Faiza Abdul (Dr. Marilyn Ahun – CHHD)
- 33 **Proteomic Profiling of Dorsal Root Ganglion in Mouse Model of Polytrauma with Spinal Cord Injury-associated Neurogenic Heterotopic Ossification**
Presented by Jiaqi Ge (Dr. Chan Gao – SIS)
- 34 **Regulatory Challenges in Canada for Meal Replacement Products for Diabetes Remission**
Presented by Eva Levin (Dr. Kaberi Dasgupta – MeDiC)
- 35 **Cross-Sectional Laboratory and Imaging Correlates of Valvular Disorders: A Study from the Courtois Cardiovascular Signature Program**
Presented by Aidan Wiazowski (Dr. Nadia Giannetti – CHAL)
- 36 **Methylation profiling supports diagnosis in undifferentiated uterine malignancies for a more tailored clinical management**
Presented by Nicole Zhang (Dr. Basile Tessier-Cloutier – CRP)

Group 7:

- 37 **Differentiating Human Bone Marrow Stem Cells Towards Ligamentogenic Lineage Using Physiological Oxygen Tensions and Glucose Concentrations for Tissue Engineering Applications**
Presented by Adi Orlov (Dr. Rahul Gawri – SIS)
- 38 **Sex specific effects of USP19 KO on disease progression in a mouse model of Alzheimer's disease**
Presented by Samara Milstein (Dr. Simon Wing – MeDiC)
- 39 **Exploring the pathophysiology of POLR3-related leukodystrophy by generating a disease model using patient-derived iPSCs**
Presented by Jiayue Yin (Dr. Geneviève Bernard – CHHD)
- 40 **Medical student career choice: a qualitative study of medical students with an interest in obstetrics and gynecology across Canada**
Presented by Renata Sabelli (Dr Shuk On Annie Leung - CRP)
- 41 **Re-wiring a hard-wired sensory neuron's synaptic connectivity**
Presented by Tamara Arenas Vázquez (Dr. Brian Chen – BRAIN)
- 42 **The role of income and education in the association between Hypertensive Disorders of Pregnancy and White matter hyperintensities**
Presented by Melysiane Marcotte (Dr. Louise Pilote – CHAL)

Group 8:

- 43 **Understanding the role of Orexin receptor 2-expressing cells in energy balance.**
Presented by Rania Mishal Khan (Dr. Paul Sabatini – MeDiC)
- 44 **The Transdifferentiating Potential of Myoblasts: Insights into the Cellular Mechanisms of Neurogenic Heterotopic Ossification**
Presented by Bavly Monir (Dr. Chan Gao – SIS)
- 45 **Racial disparities in stressful life events among women**
Presented by Nkasiobi Hossanna Nwobi (Dr. Ugochinyere Vivian Ukah – CHHD)
- 46 **Understanding The Molecular and Neural Function of Transcription Factor 20 (Tcf20)**
Presented by Chidiebere Okarah (Dr. Wei-Hsiang Huang – BRAIN)
- 47 **Impact of Social Determinants of Health on Arterial Stiffness in High-risk Preeclampsia Pregnancies**
Presented by Elspeth Skeats (Dr. Stella S. Daskalopoulou – CHAL)
- 48 **Development and in vitro validation of an automated image-based batch analysis methodology; leveraging patient-derived organoid-based assays for precision oncology.**
Presented by Xuanpeng Wang (Dr. Lorenzo Ferri – CRP)
- 49 **The QLC+ study: A Journey to Diagnosing COPD**
Presented by Sara Elatris (Dr. Nicole Ezer – RESP)

POSTER PRESENTATIONS

Elsbeth McConnell Atrium - 1001 boul. Décarie, Montréal, QC, Block E

AFTERNOON SESSION – GROUPS 9-17

Group 9:

- 1 NMDA receptors determine spine density of cortical layer-5 pyramidal cells**
Presented by Kalenga Lubembele (Dr. Jesper Sjöström – BRaIN)
- 2 The Role of Endoplasmic Reticulum Stress in ET-1 Induced Vascular Dysfunction in Hypertension**
Presented by Kalista Lam (Dr. Rhian Touyz – CHAL)
- 3 Clinical Isolates of Pseudomonas aeruginosa from Cystic Fibrosis Patients are Susceptible to Ofloxacin, Levofloxacin, Ciprofloxacin, and Moxifloxacin**
Presented by Maria Cabral (Dr. Dao Nguyen – RESP)
- 4 Risk Factors for Hospital Admission of Elderly Cancer Patients Presenting in the Emergency Department**
Presented by Harry Moroz (Dr. James Tsui - CRP)
- 5 Assessing Negative Dominance of Truncated ECI1 Enzyme in Prostate Cancer Cells**
Presented by Michael Petros (Dr. Jacques Lapointe – CRP)
- 6 Gender and regional inequities in oral and poster presentations at an international transplant congress**
Presented by Kathleen Gaudio (Dr. Shaifali Sandal – MeDiC)

Group 10:

- 7 Rapid variant classification in primary ciliary dyskinesia genes by use of zebrafish models**
Presented by Gabriel Marcoux (Dr. Thomas Kitzler – CHHD)
- 8 MEG Study of Frequency-Tagged Stimuli in Binocular and Pattern Rivalry**
Presented by Sophie Somé (Dr. Janine Mendola – BRaIN)
- 9 Effect of RORC Inhibition on PD-L1 Expression in Insulin-Producing MIN6 Pancreatic Beta Cells**
Presented by Hela Kabani (Dr. Steven Paraskevas – MeDiC)
- 10 Pharmacokinetic exploratory assessment of antimicrobials for treatment of acute exacerbations of Chronic Obstructive Pulmonary Disease in hospitalized patients colonized with Pseudomonas aeruginosa**
Presented by Juliette Begin, Andrea Tataranu (Dr. Bryan Ross – RESP)
- 1 Characterization of cell type-specific extracellular metabolites using a novel patient-derived esophageal adenocarcinoma-on-a-chip platform**
Presented by Batuhan Aksoy (Dr. Lorenzo Ferri – CRP)
- 12 T Cell-Monocyte Complexes and Related Immune Cell Perturbations in Preeclampsia: A Scoping Review**
Presented by Nicholas Katsis (Dr. Stella S. Daskalopoulou – CHAL)

Group 11:

- 13 CRISPR Cas9 mediated knock-in of landing pad into genomic safe harbour site**
Presented by Elinor (Zhuojun) Chen (Dr. Sampath Kumar Loganathan – CRP)
- 14 Novel therapeutics for heterotopic ossification (HO) induced by polytraumatic spinal cord injury (SCI)**
Presented by Zhilin Li (Dr. Chan Gao – SIS)
- 15 Quantifying Radiation-Induced DNA Damage via Track-Structure Simulations in a Nuclear DNA Model**
Presented by Zhenlun Dai (Dr. John Kildea – CRP)
- 16 Exploring the Determinants of Excess Weight Gain in Women with Gestational Diabetes: A Focus on Demographics, Food preparation skills, and Eating Habits**
Presented by Mona Sharafi (Dr. Kaberi Dasgupta – MeDiC)
- 17 An Evaluation of the Economic and Resource Burden of COPD and of Exacerbations of COPD (ECOPD) on the COPD Clinic and MUHC**
Presented by Shruti Rughani (Dr. Bryan Ross – RESP)

- 18 PXGS: a Poly-Transgene Expression System based on Mutually Exclusive Alternate Splicing**
Presented by Natasha Kamara (Dr. Brian Chen – BRaIN)

Group 12:

- 19 Varicella zoster virus serology in pediatric patients treated with biologic therapies**
Presented by Bianca Pozzebon (Dr. Christine McCusker – RESP)
- 20 Development of biodegradable and bioactive injectable hydrogel for ivd repair**
Presented by Harmeet Kaur Lotay (Dr. Lisbet Haglund and Jianyu Li – SIS)
- 21 Methylation profiling identifies three distinct clusters of small cell carcinoma of the ovary hypercalcemic type (sccoht) with specific morphological features**
Presented by Denia Hamidi (Dr. Basile Tessier-Cloutier - CRP)
- 22 Comparison of Derived Parameters from a Commercial Oscillometer to those of a Custom Written Multi-Purpose labview-Based Engineering Software**
Presented by Han Halyssa Ho, Tina Aghdam (Dr. Ron Dandurand – RESP)
- 23 Neural Markers of Consciousness in Brain-Injured Pediatric Patients Exposed to Anesthesia**
Presented by Marlo Naish (Dr. Stefanie Blain-Moraes – BRaIN)
- 24 Identifying genetic causes of unexplained familial infertility cases**
Presented by Sacha Mitchell (Dr. Rima Slim – CHHD)

Group 13:

- 25 Safeguarding the Vulnerable: Measles Vaccination and Seroprotection in Immunocompromised Pediatric Patients on Biologic Therapies**
Presented by Eva Mamane (Dr McCusker and Dr Mazer – RESP)
- 26 Optimizing Antenna Distribution for High-Quality Microwave Radar-Based Imaging in Breast Cancer Detection**
Presented by Yunxiao Zhang (Dr. Emily Porter – CRP)
- 27 Identifying Neocortical Layers with Histology**
Presented by Nada Shaath (Dr. Per Jesper Sjöström – BRaIN)
- 28 Impact of Music Therapy during Targeted Neonatal Echocardiography - A Survey of Neonatal Healthcare Professionals**
Presented by Joshua Hazan Mea (Dr. Gabriel Altit – CHHD)
- 29 A single-center observational study to assess the pharmacokinetic parameters of beta-lactams and fluoroquinolones in patients 75 and over**
Presented by Andrea Tataranu (Dr. Daniel Thirion – IDIGH)
- 30 Epigenetic Landscape of Small Cell Carcinoma of the Ovary Hypercalcemic Type (SCCOHT): DNA Methylation Profiling and Bioinformatics Analyses**
Presented by Nicole Elyas (Dr. Basile Tessier-Cloutier – CRP)

Group 14:

- 31 Role of fibroblast-specific CD109 in the regulation of skin inflammation and fibrosis**
Presented by Adel Batal (Dr. Anie Philip – SIS)
- 32 Resistive index values of the anterior cerebral artery are associated with the instantaneous levels of cerebral saturation in newborns with congenital heart defects**
Presented by Pasinee Kanaprach (Dr. Gabriel Altit – CHHD)
- 33 Exploring the Relationship Between Physical Activity and Sleep Quality in Pregnant Women with Gestational Diabetes Mellitus**
Presented by Ling He (Dr. Sushmita Pamidi – RESP)
- 34 The Role of CB2 Pathway Modulation in the Downregulation of CD47 Expression and Cell Death Caused by Cannabinoids in Jurkat Cell Line**
Presented by Lixing Wang (Dr. Cecilia Costiniuk – IDIGH)
- 35 RAI1 modulates dominance behaviour in mice by regulating interneuron signaling**
Presented by Sophia Mahiout (Dr. Wei-Hsiang Huang – BRaIN)

- 36 Effects of Standard Chemotherapy on Patients with Common Gastric Adenocarcinoma-Related Mutations**
Presented by Danyang Wang (Dr. Lorenzo Ferri – CRP)

Group 15:

- 37 Elucidating of the Effects of Near-physiological Culture Conditions on the Ligamentogenic Differentiation of Bone Marrow-derived Mesenchymal Stromal Cells**
Presented by Anastasia Vouloukos (Dr. Rahul Gawri – SIS)
- 38 BCG vaccination inhibits bone marrow erythropoiesis via IFN- γ**
Presented by Taylor Ireland (Dr. Maziar Divangahi - RESP)
- 39 Evaluation of Artificial Intelligence Chatbots in Addressing Most Searched Queries on Psoriasis**
Presented by Maxine Joly-Chevrier (Dr. Elena Netchiporouk – IDIGH)
- 40 Mapping the Claudin-3 Interactome During Neural Tube Closure in Chick Embryos**
Presented by Jerry Gao (Dr. Aimee Ryan – CHHD)
- 41 Evaluating the Effectiveness of Machine Learning Models for Detecting Undiagnosed Atrial Fibrillation in Primary Care using electronic health records: A Systematic Review**
Presented by Mhd Diaa Chalati (Dr. Samira Abbasgholizadeh-Rahimi – CHAL)
- 42 Copy number variation analysis supports diagnosis in vulvar malignant rhabdoid tumours and endometrial sarcoma for a more tailored clinical management**
Presented by Rayyan Fotovati (Dr. Basile Tessier Cloutier – CRP)

Group 16:

- 43 The Importance of Early Diagnosis of Sebaceous Cell Carcinoma of the Eyelid**
Presented by Morgan Yurchuk (Dr. Miguel Burnier – CRP)
- 44 The impact of catecholamines and inotropes on bacterial killing by antibiotics**
Presented by Mia Moghrabi (Dr. Alexander Lawandi – IDIGH)
- 45 Elucidating Mechanisms underlying Heterotopic Ossification in muscles of a mouse model of Polytraumatic Spinal Cord Injury.**
Presented by ZiXu Liu (Dr. Chan Gao – SIS)
- 46 Rare Diseases: Assessment of the impact of knowledge translation on patients and their families**
Presented by Mina Hmimas (Dr. Geneviève Bernard - CHHD)
- 47 Sex-Specific Associations of IL6R Variants with Aortic Stenosis**
Presented by Giannino Lombardi (Dr. Jamie Engert – CHAL)
- 48 Evaluating the Impact of Data Curation on Reproducibility of Extracted 11Hz Intra-Breath Oscillometry Parameters**
Presented by Maxime Baril, Gulraaj Kaur (Dr. Ron Dandurand – RESP)

Group 17:

- 49 Overlooking knee height asymmetry: Is there functional consequences?**
Presented by Aurélie Grandchamp (Dr. Louis-Nicolas Veilleux – SIS)
- 50 Association of a novel index of early-life growth conditions with chronic obstructive pulmonary disease outcomes**
Presented by Matthew Alter (Dr. Benjamin M. Smith – RESP)
- 51 Overcoming resistance: Survivin inhibitor, YM155, promotes Irinotecan-induced apoptosis in colorectal cancer**
Presented by Diana Russom (Dr. Danuta Radzioch – IDIGH)
- 52 The effect of arsenic exposure on chick embryo development**
Presented by Madison Archer (Dr. Aimee Ryan – CHHD)
- 53 Analyzing maternal biomarkers at birth for women with hypertensive disorders of pregnancy and their use in predicting postpartum blood pressure**
Presented by Connor Farrell (Dr. Natalie Dayan – CHAL)

ABSTRACTS

POSTER PRESENTATIONS

1 - Investigating the Role of Nodal During Murine Pregnancy

Chanel Gabriel^{1, 2}, Laurie Pinel², Laura Girardet², Daniel Dufort²

¹University of Sherbrooke, ²Child Health and Human Development Program, Research Institute of the McGill University Health Center, Montreal, Canada

Introduction: Successful pregnancy requires the synchronized combination of a receptive uterus and a mature blastocyst. In mice, the uterus is ready for implantation on D4.5 of pregnancy. This period is regulated by many factors, including steroid hormones and factors secreted by the glandular epithelium of the uterus. One important component is NODAL, a member of the TGFB superfamily. Our laboratory has developed a mouse model in which the gene has been specifically deleted in the uterus to study the role of NODAL during pregnancy. The conditional deletion of NODAL in the uterus reduced blastocyst implantation in female mice by 50%, resulting in reduced fertility. Our hypothesis is that NODAL plays a role in uterine receptivity during implantation. We aim to confirm NODAL deletion in knockout females and to study the expression of genes involved in uterine receptivity in both *in vivo* and *in vitro* epithelial cells organoid culture.

Material and Methods: For all the following experiments, the samples used were uterine horn tissues from pregnant (D4.5) Nodal control and Nodal knockout mice. The decrease in Nodal expression was verified by immunofluorescence on fixed, paraffin-embedded tissue slides for both groups of mice. For *in vivo* analysis, mRNA isolated from whole uterine horn tissue was used to verify expression of several receptivity genes and hormone receptors genes by quantification PCR. For *in vitro* experiments, glandular epithelial cells isolated from entire uterine tissue were cultured in 3D to enable organoid formation. Expression of the same genes were assessed in the organoids after 7 days of culture.

Results: We observed a significant decrease in NODAL protein in the epithelial cells of uterine horns in knockout mice compared to the NODAL controls. *In vivo*, the relative expression of each receptivity gene and hormone receptor gene was similar between NODAL control and NODAL knockout uteri. However, when we looked specifically at the epithelial cell organoids, we found a significant decrease in the knockout uteri of the expression of several receptivity genes, notably for *Lif*, *Ihh*, *Muc1* and *Msx1* as well as the hormone receptors gene *Pr* and *ESR-1* when comparing to the control.

Conclusions: The differences between *in vivo* and *in vitro* results can be explained by the fact that uterine tissue is composed of many different cell types, justifying the interest in isolating individual cell types, and evaluating them separately. Indeed, qPCR analysis of epithelial cell organoids showed altered expression of many receptivity genes, suggesting that NODAL has a key role in endometrial receptivity. As there are numerous hormonal changes in endometrial tissue during implantation and regulation by stromal cells which are absent in the *in vitro* organoid cultures, the next steps would be to assess the response of epithelial cells *in vitro* when subjected to this hormonal fluctuation in knockout mice and to study the behavior of our 3D culture model following the addition of stromal cells.

Source of Funding: Canadian Institutes of Health Research to Dr. Daniel Dufort.

2 - Constructing a Plasmid to Model PFA Ependymomas in Mice Models

Noa Bouzaglo¹, Sampath Loganathan^{1, 2, 3}

¹Cancer Research Program, Research Institute of the McGill University Health Centre, ²Department of Otolaryngology, Head and Neck Surgery, ³Department of Medicine, Division of Experimental Medicine, McGill University, Montreal, Canada

Background: Ependymomas are tumours in the glial cells of the central nervous system, being histologically similar but genetically different, based on the region of origin of the primary tumour. This distinction in the molecular makeup and location of origin of the ependymoma is what defines its classifications. One of the subtypes is Posterior Fossa group A ependymomas, hereby referred to as PFA. PFA occurs primarily in infants and presents with an extremely poor ten-year progression-free survival rate. It is considered to be a very aggressive type, being treated with radiation and therapy but recurring within two years in the majority of cases. A specific challenge that makes PFA so difficult to understand is that it is genetically silent, meaning there is no specific mutation directly associated with it. However, many studies have found that it is strongly correlated to the overexpression of EZHIP (Enhancer of Zeste Homolog Inhibitory Protein) and epigenetic dysregulation. EZHIP is a protein that inhibits the activity of the Polycomb Repressive Complex 2 (PRC2), which is responsible for trimethylating histone H3 on lysine 27 (H3K27me3), a key epigenetic mark for gene repression. In PFA ependymomas, overexpression of EZHIP mimics the effect of H3K27M mutations found in other types of gliomas, leading to a global reduction in H3K27me3 levels. This inhibition of PRC2 activity by EZHIP results in epigenetic dysregulation that promotes tumorigenesis in these ependymomas. The lack of specific genetic driver mutations for this disease has made modelling PFA ependymomas very difficult. The goal of this experiment is to model the overexpression of EZHIP in mice, to better understand the mechanism of PFA ependymoma. Eventually, this model can help establish better treatments for patients with the disease.

Methods: To establish a mouse model for PFA ependymomas, we first must construct a plasmid to overexpress EZHIP. The PiggyBac vector is used to construct the plasmid. PiggyBac plasmids are a type of transposon system used for genetic modification. They enable the stable integration of a gene of interest into the genome of a host cell. Using the EZHIP gene as an insert in the plasmid, if it is successfully integrated, it will overexpress the EZHIP protein in the transfected mice. mRFP was also incorporated in the plasmid, to be used as a quantitative reporter gene of EZHIP transcription.

Results: The construction of the plasmid to overexpress EZHIP in a mouse model is ongoing. Once completed, this plasmid, incorporating the EZHIP gene and mRFP as a reporter, will enable stable genomic integration and overexpression of EZHIP protein in transfected mice.

Conclusions: Our ongoing work on constructing the plasmid for EZHIP overexpression in a mouse model will soon enable us to proceed with stable genomic integration and subsequent protein expression analysis. Future steps include validating the integration and expression efficiency, followed by in vivo studies to investigate the functional role of EZHIP in Posterior Fossa type A ependymomas.

Source of Funding: The funding for my summer internship was generously provided by the Mach-Gaensslen Foundation of Canada Student Grant.

3 - Machine Learning Analysis of Arterial Stiffness Trends throughout Pregnancy to Predict the Development of Preterm, Term and Postpartum Preeclampsia

Allison Engo¹, Ido Zamberg (MD, MEHP)^{2,3}, Maria Matossian³, Helena Papacostas-Quintanilla (PhD)^{1,2}, Stella S. Daskalopoulou (MD, PhD)^{1,2,3}

¹Faculty of Medicine, McGill University, ²Vascular Health Unit, Research Institute of the McGill University Health Centre, ³Division of Experimental Medicine, Department of Medicine, McGill University Health Center

Introduction and Background: Preeclampsia (PrE), a serious disorder of pregnancy, is characterised by high blood pressure and dysfunction of end organs like the kidneys and liver. It affects approximately 5-8% of pregnancies globally and can lead to devastating maternal and fetal outcomes. Historically, PrE is considered a single condition with varying degrees of severity. However, recent evidence supports classifying PrE based on its time of onset into preterm (before 34 weeks of gestation), term (after 34 weeks) and postpartum (following delivery). These subtypes of PrE vary in severity and presentation. For instance, compared to term PrE, preterm PrE is associated with a higher risk of maternal and neonatal morbidity and mortality. Early prediction of PrE and its subtypes could result in better prevention strategies, health resource utilisation and better patient outcomes. However, despite significant advancements in medicine, accurate early prediction of PrE remains a challenge. Current screening methods, including Uterine Artery Doppler (UAD) and analysis of angiogenic factors, provide low to moderate predictive ability for PrE. In our previous REVEAL study, arterial stiffness (AS) parameters, a validated indicator of vascular health, predicted the development of PrE with high ability (AUC=0.83), providing evidence for its utility. These results are currently being validated in our larger multinational PULSE study. The present research aims to assess the predictive ability of arterial stiffness measurements for PrE and its subtypes in the first and second trimesters of pregnancy.

Methods: We performed an *ad-hoc* analysis using data from REVEAL and PULSE. In both studies, AS measurements were taken during trimesters 1 and 2 (10-14 and 18-24 weeks). Data was fitted, trained and evaluated after feature selection using four distinct machine learning algorithms (Support Vector Machine, Random Forest, Logistic Regression and Gradient Boosting) to assess the best-performing model for each of the four outcomes (PrE, pretermPrE, termPrE, postpartumPrE) in each trimester. Performance for each model was reported by the Area Under the Curve (AUC) measure.

Results: Data from 310 participants were analysed; 12.58% were diagnosed with PrE(n=39) within which 25.6% had preterm PrE(n=10), 53.8% had term PrE(n=21) and 20.6% had postpartum PrE(n=8). The best model for predicting overall PrE had an AUC of 0.75 in the first trimester and 0.76 in the second. For preterm PrE, the best model had an AUC of 0.81 in the first trimester and 0.72 in the second. For term PrE, the best model had an AUC of 0.77 in the first trimester and 0.75 in the second. Models for postpartum PrE did not perform well (AUC<0.55).

Conclusion: AS was shown to have high predictive ability for PrE and its subtypes as soon as the first trimester of pregnancy with highest values for preterm PrE. Further research will be performed to validate the use of AS measurements as an early predictor for PrE and its subtypes in PULSE and other larger cohorts. Moreover, the additive predictive ability of AS when considering other clinical and biological markers will be assessed.

Source of Funding: This study was funded by the Canada Institutes for Health Research (Project#168918), Fonds de Recherche du Québec-Santé (Project#25045), and the Heart and Stroke Foundation of Canada (Project#000437)

4 - Development of a ChatGPT-Powered Crisis and Suicidal Ideation Management Module for an HIV Self-Management Chatbot

Sebastian Villanueva¹, Yuanchao Ma², Sofiane Achiche³, Bertrand Lebouché³, David Lessard⁴

¹Summer Student, ²PhD Candidate, ³PI, ⁴Research assistant

Background: MARVIN is a chatbot promoting self-management of medication among people with HIV (PWH) and currently providing support for medication adherence and HIV-related general knowledge. PWH face significant stigma and mental health challenges (e.g., stress, depression, and isolation), and are at greater risk of distress than the general population.

Objectives: To enhance MARVIN's ability to respond to users' potential 'extreme messaging' (e.g. messages suggesting suicidal thoughts or including self-harming or discriminatory components). Sub-objectives are to 1) develop a classification algorithm of extreme messaging, 2) integrate this algorithm into MARVIN, and 3) assess its usability and impacts on patient-chatbot communication, including conversation clarity and user satisfaction.

Methods: We integrated three public hate speech databases from an online catalog (hatespeechdata.com) mixed with recorded MARVIN-user conversation dataset and MARVIN synthetic data (e.g. permutations of our own data), to train ChatGPT to identify three categories of messages: self-harm, insults, and normal (e.g., messages which intents are not self-harm or insult). We prompt-tuned the model and tested its performance with different prompts and the one-shot prompting technique. We quantified its performance with recall, precision, accuracy, and F1 score metrics. We then integrated ChatGPT into MARVIN's classification tree through requests to the OpenAI servers. We constructed a 2-hour test guide of 14 scenarios and asked six testers, including three PWH and three professionals (e.g. two engineers and one doctor), to do each scenario, and then to fill out a two-item on conversation clarity and user satisfaction.

Results: Using one-shot prompting and a prompt using the CO-START framework, ChatGPT attained a value of 96% across all the metrics. The hybrid ChatGPT-MARVIN model successfully generated appropriate responses to extreme messaging with emergency contacts, while relying on MARVIN's original responses for messages with 'normal' intentions. When applying scenarios, testers considered MARVIN's responses as clear and concise, and were satisfied with the responses and overall experience.

Conclusion: This 'anti-extreme module' represents the first filter for MARVIN. Large language models such as ChatGPT can help identify extreme intentions like self-harm and insults and to generate appropriate responses for healthcare chatbots. Providing users with non-judgmental support could help alleviate stigma and mental health challenges. These results could be used to further modernize self-management for PWH using artificial intelligence.

5 - CT scan derived mean curvature of isophotes (MCI) for the detection of alpha-1 antitrypsin deficiency (AATD)- related emphysema

Zlatitsa Todorova^{1, 2}, Peter Savadjiev³, Luis H. Gonzalez Torres¹, Ronald J. Dandurand^{2, 4, 5}

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Introduction: COPD, a lung disease comprising emphysema, gives rise to airflow limitations and dyspnea. Usual COPD, which can arise from environmental factors such as smoking, differs from alpha-1 antitrypsin deficiency (AATD)-related COPD, with the latter resulting from mutations of the genes encoding for the production of the alpha-1 antitrypsin (AAT) protein. Oscillometry, a more sensitive form of lung functioning test compared to conventional spirometry methods, has shown that mechanical changes associated with AATD-related emphysema are more evenly distributed than the mechanical changes associated with regular COPD-related emphysema. Quantitative computed tomography (qCT) is currently used to quantify emphysema in COPD patients. Furthermore, it has been validated that the use of MCI, which involves geometrically transforming original CT images, allows for better separation between healthy lung tissue and lung tissue of COPD patients in the early stages of emphysema. As such, this project proposes to explore the use of the MCI to separate AATD-related and usual COPD-related emphysema. It is hypothesized that the usage of the MCI will allow for superior separation of AATD-related and usual COPD-related emphysema compared to standard quantitative CT radiomics.

Materials and Methods: Two study groups consist of patients affected by usual COPD and patients affected by AATD-related COPD. The patient database contains the information listed above from 134 "usual" COPD and AATD-related COPD patients (the differentiation was based on patient AAT serum levels). Thoracic CT scans will be exported as dicom files using the OsiriX software. The Chest Imaging Platform plug-in for the 3D Slicer software will be used to quantify emphysema by evaluating lung density. Measurement of the MCI from the dicom files will be done using the laboratory's in-house custom software. All relevant data, including patient-reported outcomes (CAT, MRC, CB and AER questionnaires), emphysema quantification (LAA%-950, Perc15, lung volume and ULZ:LLZ ratio metrics) and MCI measurements, will be collected and subjected to further analysis through Stata and JASP. Evaluation of data distributions, group differences and univariate correlations will be conducted to examine whether the MCI can find statistically significant differences between usual COPD-related and AATD-related emphysema.

Results: No results are available yet. The project is currently at the step of the MCI data extraction. Following the MCI data extraction, statistical analysis on the quantitative CT and MCI metrics will be run to obtain results. All of these steps are expected to be completed before the presentation.

Conclusions: It is important to develop a methodology that allows for efficient and early diagnosis of AATD, as patients with established respiratory disease are subject to a median delay of 7 years after symptom onset before they receive a positive AATD diagnosis. Should we have a positive outcome, we will have access to a larger and more comprehensive data set from Dublin, Ireland, for further validation.

Source of Funding: This project is supported by the Dandurand lab.

6 - The Role of TNF in Synaptic Function from Neuron and Glia Culture Models

Fedgi Dony Gaspard^{1,2}, Zahra Abbasi^{1,3}, Adora Wang^{1,3}

¹ Research Institute of the McGill University Health Centre, ² Physiology major, McGill University, ³ McGill university

Communication between neuron and glial cells is bidirectional, neuromodulators produced by neurons can stimulate the glia, which in turn can respond through several factors such as tumor necrosis factor (TNF). TNF is a proinflammatory cytokine involved in maintaining synaptic function. Neuromodulators trigger different signaling pathways in glia, predominantly through G-protein coupled receptors (GPCRs). In this experiment, through the manipulation of GPCRs in astrocytes, we characterized the signaling pathway underlying different types of receptors and their effects on TNF expression using quantitative polymerase chain reaction (qPCR). Our findings suggest that the G-protein-mediated activation and inhibition in glia are reversed from what seen in neurons. Typically, in neurons, activation of the Gi pathway leads to inhibition, while activation of the Gq and Gs pathways leads to neuronal activation. However, in our studies with astrocytes, we observed the opposite effect: Gi activation results in increased activity, whereas Gs and Gq activation led to decreased activity, at least in terms of TNF production.

Moreover, TNF has an important role in one special type of homeostatic synaptic plasticity (HSP), following activity blockade. Its activity leads to the strengthening of the synapses via AMPA receptors trafficking. We know that pyramidal neurons exposed to TNF for one hour exhibit synaptic upscaling, through the exocytosis of Glutamate receptor-1 (GluR-1). Here, we aim to replicate these conditions by chronically treating cortical neurons with TNF for durations ranging from one hour to three days. Using immunostaining, we can quantify the expression of GluR-1 in the cells after the different treatments. We expect a significant increase in GluR-1 expression in cortical neurons treated with TNF for 1 hour up to 3 days.

7 - The Role of Innate Immune Cells in Colorectal Cancer Liver Metastases

Benjamin Tordjman¹, Anastasia Tsatoumas^{1, 2}, Jessica Bloom¹, Stephanie Petrillo^{1, 3}, Anthoula Lazaris^{1, 3}, Zu-Hua Gao⁴, Peter Metrakos^{1, 3}

¹Cancer Research Program, McGill University Health Centre Research Institute, ²Department of Anatomy and Cell Biology, McGill University, ³Department of Surgery, McGill University, ⁴Department of Pathology, University of British Columbia

Background: Colorectal cancer is the third most diagnosed cancer worldwide and among the deadliest forms as 50% of patients will develop liver metastases, leading to a poor prognosis. Colorectal liver metastases exhibit various histological growth patterns (HGP), particularly the desmoplastic and replacement types. Favouring an angiogenic blood supply, a desmoplastic HGP tumor is characterized by a band of desmoplastic tissue separating the cancer cells from the hepatic parenchyma. Conversely, a replacement HGP tumor infiltrates the hepatic parenchyma, displacing resident hepatocytes, and relies on vessel co-option as a means of vascularization. Our previous research indicates that desmoplastic HGPs exhibit a greater concentration of adaptive immune cells, whereas replacement HGPs are associated with a greater presence of innate immune cells. Innate immune cells, particularly macrophages and neutrophils, are essential in tumor growth, fostering a microenvironment that can hinder or promote liver metastasis growth. This research examines how innate immune cells promote vessel co-option in the vascularization of colorectal cancer liver metastases by influencing tumor histological growth pattern and motility. Moreover, this study aims to demonstrate that depleting innate immune cells, particularly macrophages, affects tumor size and vascularization mechanisms, specifically vessel co-option or angiogenic growth patterns.

Methods: The development of liver metastases was simulated in Balb/C mice by the formation of replacement liver metastases through intrasplenic injections of one million CT26 mouse colorectal cancer cells. Following the establishment of tumors in the mouse livers 10 days post-injection, mice were either treated intraperitoneally with 200 μ L of clodronate liposomes, a macrophage depletion drug, or PBS liposomes, which served as the control group. Clodronate liposomes are ingested by macrophages via endocytosis and induce apoptosis by inhibiting mitochondrial ADP/ATP translocase. Tissue samples were analyzed using haematoxylin and eosin (H&E) staining and immunohistochemistry (IHC) with the macrophage marker F4/80.

Results: IHC using the antibody F4/80 confirmed the successful depletion of macrophages in mice treated with clodronate liposomes, while the same staining indicated that macrophages were preserved in the control group. The PBS-treated mice possessed multiple tumors yet maintained normal-appearing liver parenchyma, yet the clodronate-treated mice unexpectedly had necrotic tumors and demonstrated severe liver damage adjacent to where the tumor was located. The clodronate-treated mice also did not survive longer than 5-6 days after treatment. To confirm that this was not a general toxic effect of the clodronate, mice with no liver tumors were also treated with clodronate. These mice had normal looking livers, with no damage.

Conclusions and Future Directions: Our work demonstrates that macrophage depletion, via clodronate induces a toxic effect in the liver of mice with tumors only. To confirm that this may be unique to clodronate as it induces apoptosis of macrophages, further research will explore the use of the anti-CSF1R antibody, an inhibitor of the colony stimulating factor 1 receptor on macrophages which limits macrophage function without inducing apoptosis, unlike clodronate liposomes.

Sources of Funding: CRS Operating Grant

8 - Patient and service outcomes of administering an ePROM of barriers to adherence to antiretroviral therapy to people with HIV through a patient portal

MHD Amir Chalati¹, David Lessard¹, Yuanchao Ma¹, Kim Engler¹, Ashkan Baradaran¹, Tarek Hija², Alexandra de Pokomandy¹⁻³, Cecilia T. Costiniuk¹, Joseph Cox¹, Bertrand Lebouché¹⁻³

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Introduction: Adherence to antiretrovirals (ART) by people with HIV (PWH) is crucial, however, many face obstacles that go undiscussed with health professionals. We used the patient portal (Opal) to administer the I-Score, a 7-item electronic patient-reported outcome measure (ePROM) of barriers to ART adherence.

Methods: We enrolled adult PWH on ART, speaking French or English, owning a smartphone, willing to use the patient portal, with a history of adherence issues. Participants completed the I-Score on the patient portal up to two days before visits with their physician at Baseline (T1), 3 months (T2), and 6 months (T3). We collected patients' sociodemographic information at T1, and HIV viral loads at T1 and T3. At each visit, patients reported ART adherence, and physicians completed a checklist of actions undertaken based on I-Score results. Patient outcomes at T1 and T3, included frequencies and proportions of HIV viral load undetectability, and mean scores for self-reported adherence (score of 1 to 5) and adherence barriers (score of 1 to 10) over the past month. For service outcomes, we report frequencies and proportions of clinical visits where physicians took actions based on I-Score results.

Results: Out of 26/32 participants who completed the intervention, 11/26 (42%) were female; 14/26 (54%) aged ≥ 50 years; and 8/26 (31%) had an income below \$19,999. Most patients (23/26) had an undetectable viral load at T1 and T3. Concerning domains of adherence barriers, mean scores decreased for: Thoughts/Feelings (T1=2.9/10 to T3=2.3/10), Habits/Activities (1.8;1.7), Medication (2.1;1.5), and Health (2.0;1.3), but increased for: Social (2.5;2.9) and Economic Situation (2.4;2.6), and Care (1.3;1.4). Average self-reported adherence increased from T1 (4.11) to T3 (4.19). Physicians ordered new tests for 10/26 (38%) patients, changed the medication plan of 7/26 (27%) patients, and referred 14/26 (54%) patients to a specialist.

Conclusions: Administering the I-Score on a patient portal is feasible and appears to improve patient and service outcomes, yet with slight fluctuations. Further research is recommended for a more robust understanding of its efficacy.

Source of funding: CIHR Canadian HIV Trials Network.

9 - Two-photon optogenetic mapping of connectivity in layer-6 pyramidal cells of mouse primary motor cortex

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Background: Connectivity patterns of neocortical microcircuits determine how they process information. Yet, comprehensive, large-scale maps of cortical circuits are challenging to produce. The gold-standard approach for characterizing connectivity - multiple whole-cell recordings - has throughput limitations that restrict the number and type of connections that can be sampled during an experiment. To solve this problem, our lab developed optomapping, which combines optogenetic stimulation and whole-cell recording to dramatically increase the throughput of connectivity sampling. We previously optomapped mouse primary visual motor cortex (V1) and are now exploring primary motor cortex (M1) to see how microcircuits in these functionally distinct cortical areas differ. Microcircuit connectivity in layer 6 (L6) pyramidal cells (PCs) of M1, a cortical output layer, has yet to be characterized. This project therefore aimed to optomap excitatory inputs to M1 L6 PCs.

Methods: At postnatal day (P) 0-2, *Emx1^{cre/cre}* mice were transcranially injected with AAV-CAG-DIO-ChroME-ST-P2A-H2B-mRuby3 to express the excitatory opsin, ChroME, in PCs. Acute brain slices containing M1 were harvested from injected animals at P19-26 and L6 PCs were targeted for whole-cell recording. While the patched M1 L6 PC was recorded, nearby ChroME-positive PCs were activated with three spiral scans at 30 Hz, using a Ti:Sa laser tuned to 1040 nm. If the patched PC was postsynaptic to a stimulated PC, three excitatory postsynaptic potentials were recorded. Optomapping was repeated for neighboring fields of view across the cortical thickness for a 200-micron wide cortical column centered on the patched cell. The postsynaptic cell was classified using electrophysiological and morphological properties.

Results: Of 509 tested PC to L6 PC connections, 14 PC to L6 PC connections were found ($n = 3$ cells). These connections were distributed between only L4, L5, and L6, with no difference in the number of connections between layers (ANOVA, $F(2,6) = 1.314$, $p = 0.336$). There was also no difference found between L6 V1 connectivity ($n = 15$ cells) and L6 M1 connectivity (generalized linear mixed model, $\chi^2(1) = 0.9533$, $p = 0.329$).

Conclusions: These preliminary findings indicate that M1 L6 PC connectivity resembles that of V1 L6 PCs. This aligns with prior optomaps of L2/3 and L5 of M1 connectivity, which revealed only slight differences as compared to V1. Taken together, these findings suggest that microcircuits in areas as functionally distinct as M1 and V1 are in fact surprisingly similar. Future directions for this project will be to sample more postsynaptic L6 PCs, and to map connectivity onto L6 inhibitory interneurons. In summary, optomapping provides a more comprehensive understanding of cortical microcircuits.

Funding: The Sjöström lab acknowledges funding from the CFI, the CIHR, FRSQ, and NSERC.

10 - The Toxicological Effect of Cannabis Smoke in Alveolar Macrophages

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Background: Cannabis has been legalized for recreational use in Canada since 2018, despite the unknown health impacts. The most common way to consume cannabis is by smoking the dried plant. When cannabis smoke is inhaled, one of the first cell types to encounter the foreign particles are alveolar macrophages. Alveolar macrophages function to maintain lung homeostasis through efferocytosis, debris clearance, and phagocytosis. Our previous research showed that cannabis smoke downregulates proteins related to phagocytosis in the lungs through an aryl hydrocarbon receptor (AhR) dependent manner. AhR is a transcription factor that acts as a master regulator for various cellular functions and is strongly activated by polycyclic aromatic hydrocarbons found in cannabis smoke. Thus, this study investigates the effect of cannabis smoke extract (CaSE) on the phagocytic function of alveolar macrophages and the role of AhR in this process.

Methods: CaSE was prepared by bubbling THC-dominant cannabis smoke in 100% ethanol, filtering it through a 0.45µm filter, and diluting it with Dulbecco's modified Eagle's medium. The concentration of Δ^9 -tetrahydrocannabinol (THC) in our CaSE was 557.6µg/mL as measured by high-performance liquid chromatography. THC was used as a marker for CaSE concentration. MH-S cells were treated with CaSE dilutions containing 500 to 4000ng/mL of THC. Cytotoxicity and metabolic stress were measured by the lactate dehydrogenase (LDH) and 3-(4,5-Dimethylthiazol-2-yl)-2,5-Diphenyltetrazolium Bromide (MTT) assay, respectively. CaSE containing 1000ng/mL THC was selected for subsequent experiments as it minimized cytotoxicity and metabolic stress.

Ongoing experiments include treating MH-S cells with CaSE containing 1000ng/mL THC for 3, 6, and 24 hours. Reverse transcriptase quantitative polymerase chain reaction (RT-qPCR) will be performed on AhR battery genes, specifically CYP1A1, CYP1B1, and AhRR to measure AhR transcriptional activity. The incubation time with the highest AhR activation will be used in subsequent experiments.

Next, the phagocytic activity of CaSE-exposed MH-S cells against mCherry fluorescent *Escherichia coli* will be measured using flow cytometry and validated with confocal microscopy. All experiments will be repeated using AhR knockdown MH-S cells to evaluate AhR dependency of phagocytosis after CaSE exposure.

Results: We found that CaSE induces respiratory stress in MH-S cells at a lower dose than cytotoxicity. MTT assessment found a significant decrease in mitochondrial function beginning at 1500ng/mL THC, while the LDH assay indicated cytotoxicity beginning at 2500ng/mL THC. CaSE containing 1000ng/mL THC was used for subsequent experiments as it minimized cytotoxicity and metabolic stress while still exerting a cellular response. Ongoing experiments aim to determine the optimal CaSE exposure duration for AhR activation, establishing the foundation for future investigations of the effects of CaSE on alveolar macrophage phagocytic function.

Conclusion: This work indicates that cannabis smoke extract induces metabolic stress in alveolar macrophages. This aligns with literature suggesting that cannabinoids and cannabis smoke induce apoptosis in various cell types by disrupting mitochondrial function. Moreover, mitochondrial dysfunction has been shown to impair macrophage function. This is important in alveolar macrophages as they are largely responsible for maintaining lung homeostasis. Future work will examine the effect of CaSE on the phagocytic function in alveolar macrophages.

11 - Sex Differences in the Impact of Hypertension on the Heart, Brain, and Kidney: A Systematic Review

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Introduction: Hypertension affects over 30% of adults worldwide and is a leading risk factor for diseases of the heart, brain and kidney. It is thought that the role of hypertension in organ damage across the cerebro-cardio-renal axis could be explained by small vessel disease (SVD) but understanding of the various organ interactions that define hypertension-mediated organ damage (HMOD) remains limited. Therefore, the objective of this systematic review is to appraise the state of knowledge on the role of hypertension-induced SVD in the heart, brain, and kidney, with a focus on sex differences.

Methods: We performed a systematic review of studies assessing the relationship between sex, hypertension and SVD in the heart, brain, and kidney in human adults on June 11, 2024. Our literature search used the following databases: Cochrane Library including CENTRAL, Embase, Embase Classic, MEDLINE, and Web of Science. Observational studies and randomized controlled trials were included, provided they were in English and examined the relationships between sex, hypertension, and SVD in at least two of the three organs of interest. This ongoing review is registered with PROSPERO (ID: CRD42024562358).

Preliminary results: We identified 13,073 studies after the exclusion of duplicates. At the present stage of screening, our preliminary analysis of studies that satisfy the established inclusion criteria suggests that very few studies focus on the multi-organ impact of hypertension on heart, brain, and kidney outcomes. Most studies tend to focus on establishing links between hypertension and a single organ in isolation. Moreover, sex-stratified analyses also appear to be infrequent, which limits the potential to establish sex-specific HMOD patterns. The data extraction process for this systematic review will target data relating impacts of hypertension in the heart, brain, and kidney and aim to present evidence shedding light on hypertension-mediated mechanisms of multi-organ damage.

Expected Outcomes: This systematic review seeks to examine the multi-system impacts of hypertension, thus intending to move beyond the traditional method of studying isolated organ dysfunction. While the literature search was designed to be broad in the scope of HMOD types it covers, data synthesis on multi-organ relationships in hypertension-mediated organ damage from SVD is likely to be limited by a sparse evidence base. The assessment of sex differences in this matter is expected to be associated with an even narrower data set. Nonetheless, identifying novel connections and patterns in HMOD across the heart-brain-kidney axis could allow for improved cardiovascular risk assessment and more personalized treatment strategies, especially when considering sex-specific differences.

Source of Funding: This systematic review was supported by the Heart and Stroke Foundation of Canada*.

12 - Diagnostic Potential of Spectral Oscillometry versus Spirometry in Asthma

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Background: Confirmation of spontaneously variable or methacholine-induced airway constriction as measured by spirometry is required to confirm a diagnosis of asthma. However, spirometry requires more than 75% of small airways to be dysfunctional before expiratory airflow limitation (EFL) becomes apparent. Spectral oscillometry, an alternative method, is a simpler, faster, and easier-to-perform lung function test that detects EFL when only 20% of small airways are dysfunctional. We hypothesized that spectral oscillometry may obviate the need for more complicated spirometry-based tests such as the methacholine challenge in some asthma subjects.

Methods: We conducted a retrospective chart review of 733 subjects from a community practice. Complete data including biometrics (age, sex, smoking history, weight, height and BMI), spirometry (methacholine challenge), spectral oscillometry (CVR5, R5, R5-20, X5, FRES, and AX) and pulmonary function tests (PFT) was available for 46 patients. ECSC and Berger normative data were used for PFT and spectral oscillometry respectively. Subjects were divided into two groups based on their methacholine reactivity status, with a threshold of 0.40 mg for separation. The measurements of the spectral oscillometry parameters for these groups were then plotted using a boxplot to visualize the distribution between reactive and non-reactive subjects. Inter-group differences were tested using the Mann-Whitney U (MWU) test in JASP to determine the significance of the findings.

Results: The 46 subjects (15M,31F) yielded 24 reactive subjects (1M:2F) and 22 non-reactive subjects (7M:15F). Among all the spectral oscillometry parameters, a statistically significant difference was observed between reactive and non-reactive subjects in R5 measurements, with a p-value of 0.017. The median R5 value for non-reactive subjects was 3.37 cmH₂O/L/s with an IQR of 1.32, while the median for reactive subjects was 4.47 cmH₂O/L/s with an IQR of 2.08. The boxplot analysis showed that reactive subjects generally had higher R5 values. An R5 threshold of approximately 5.50 cmH₂O/L/s was observed, above which all individuals were reactive, suggesting that for subjects with R5 measurements above this threshold, the methacholine challenge might not be necessary to confirm a diagnosis of asthma.

Conclusions: The study shows that spectral oscillometry, particularly R5 measurements, significantly differentiates between reactive and non-reactive subjects, indicating its potential in diagnosing asthma. However, it cannot replace the methacholine challenge alone. An R5 threshold of approximately 5.50 cmH₂O/L/s, above which all subjects are reactive, suggests that spectral oscillometry might reduce the need for the methacholine challenge in some cases. Nonetheless, further validation is required. Future research will integrate lung volumes into the study, develop a custom software to facilitate chart review and identify more patients who have undergone the methacholine challenge and spectral oscillometry but tested negative for asthma, and investigate intra-breath (IB) oscillometry parameters to enhance diagnostic accuracy.

Source of funding: This research is supported by the Dandurand Pneumology Clinic.

13 - The Impact of POLR3-related Leukodystrophy on Non-Affected Family Members: A Qualitative Study

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Background: RNA polymerase III-related leukodystrophy (POLR3-HLD), also known as 4H leukodystrophy, is one of the most common hypomyelinating leukodystrophies, characterized by abnormal deposition of white matter during development. It is caused by biallelic pathogenic variants in genes encoding subunits of RNA polymerase III, including *POLR3A*, *POLR3B*, *POLR1C*, *POLR3K*, and *POLR3D*. Disease onset typically occurs in childhood and runs a progressive, debilitating, and often fatal course. Given its rarity, complexity, and progressive nature, family members of affected individuals likely face significant challenges. Therefore, we sought to explore the experiences of parents and siblings of patients with POLR3-HLD to better understand their specific needs and identify modifiable factors to alleviate family burden and enhance quality of life.

Methods: Semi-structured interviews were conducted with parents and siblings of patients with POLR3-HLD, focusing on financial, emotional, and psychosocial impacts on parents, as well as siblings' relationship with their affected sibling(s) and the psychosocial impacts they may have experienced. Interviews were recorded, transcribed, coded, and analyzed using reflexive thematic analysis to identify themes related to the impact on and experiences of family members.

Results: 19 semi-structured interviews with 24 parents and 9 interviews with 9 siblings were completed between March-October 2023 and February-May 2024, respectively. Four themes were developed from parents' experiences: extensive caregiver burden, emotional and psychosocial challenges, the importance of parental self-health, and comfort in the leukodystrophy community. Parents often play multifaceted and demanding roles, encountering challenges in their personal, financial, and social lives. With limited available knowledge, parents are often left grappling with uncertainties and feelings of anxiety, frustration, and guilt. They also acknowledged the necessity of prioritizing self-care. The leukodystrophy community emerged as crucial, offering parents comfort, guidance, and support. Three themes were identified from sibling interviews: the spectrum of emotional impacts, limited knowledge about POLR3-HLD, and adapting to their siblings' needs. Siblings faced similar emotional challenges which appeared to differ along age-specific lines; younger siblings demonstrated a casual acceptance of their sibling's condition. Siblings also presented with limited knowledge about POLR3-HLD, however, they recognized their siblings' needs and actively participated in daily care.

Conclusions: This study provides a comprehensive understanding of the family experience, identifying the common challenges and specific needs of parents and siblings of patients with POLR3-HLD. It highlights the importance of improving the global care offered to this vulnerable patient population.

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14 - Investigating Antimicrobial Activity of Bacterial Isolates from Canadian High Arctic Soil

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Introduction: 4.5 million deaths globally each year are associated with antimicrobial resistance (AMR). This AMR crisis has made it evident that there is a need to discover novel antimicrobial compounds, as resistance to antibiotics currently used in clinical settings is on the rise. With most antibiotic compounds used clinically today coming from soil actinomyces, the soil has proven to be a prosperous environment to search for antimicrobial compounds. Furthermore, extreme environments like the Canadian high Arctic present unique environmental pressures that have the potential to harbour bacteria producing new compounds.

Methods: Here we investigate 13 Arctic isolates for their antimicrobial capabilities against human pathogens. 13 Arctic isolates were screened in co-culture assays against 7 pathogens, including antibiotic-resistant strains. Crude extracts of the two prioritized strains, 5-2018 and 57-2018, were generated via organic extraction with ethyl acetate and were tested against 4 pathogenic bacteria. The strains were grown in both R2A media and TSB media to determine the optimal culture conditions for antimicrobial production. To gain insight into these extracts' potential mechanism of action, we used a bioreporter assay to screen for potential modes of action. Finally, the strains were sequenced to see if they contained any biosynthetic gene clusters of interest

Results: 5-2018 displayed activity against 9 ESKAPE pathogens. 57-2018 displayed activity against 10 ESKAPE pathogens and 4 Carbapenem-resistant pathogens. When grown in TSB media, supernatants of both 5 and 57 were capable of killing more *E.coli*Δ*tolC* bacteria than when grown in R2A. Both 5-2018 and 57-2018 had BGCs with 76% similarity to histicorrugatin, a cell wall synthesis inhibitor and 40% similarity to aryl polyene Vf, which disrupts cell membranes. Furthermore, 57-2018 had a BGC with 100% similarity to labradorin, an indole alkaloid known to inhibit bacteria growth.

Conclusions: Optimizing growth conditions and better comprehending the effects of isolates 5 and 57, will further guide the direction in which this project will proceed to achieve optimal results. 5 and 57, along with more arctic bacteria isolates, will be further screened to see if they produce novel antimicrobial compounds using optimal growth conditions. Moving forward, extracts with promising antimicrobial effects can be fractionated to further understand their antimicrobial effects, and hopefully get us closer to developing novel antibiotics.

15 - The Dynamics of Suppression in Interocular Synchronicity in Human Vision

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Background: Binocular combination is a process that fuses slightly different images from the two retinas into a single, unified cyclopean image. It consists of two sub-processes: binocular summation and interocular suppression. For proper integration of visual information within the central nervous system, summation and suppression need equal spatial input from both eyes and temporal synchronization across the eyes. However, when these processes are desynchronized, they may not function properly. Desynchronized processes can impair binocular vision, such as in the case of amblyopia, a visual developmental disorder associated with interocular processing differences. Temporal deficits in amblyopia can negatively impact motion perception and visuospatial attention, to name a few. Research on the temporal dynamics of binocular combination and on whether both components of binocular combination are equally affected by desynchronization remain limited.

Purpose: A previous study investigating the impact of temporal desynchronization on interocular suppression observed minimal suppression when stimuli were presented simultaneously for 8ms. Given the highly transient nature of the stimuli used in that study, this research project aims to explore the effect of using stimuli with longer durations to gain a better understanding of the dependence of the previously observed effect on stimulus duration. We aim to enhance our understanding of the temporal dynamics of suppression and uncover the role of interocular synchronicity in binocular combination, potentially leading to new treatments for amblyopia through eye re-synchronization.

Methods: We used a dichoptic masking paradigm employing a two-alternative-force-choice task to measure suppression in normal sighted participants binocularly. On a passive 3D screen, a Gabor target was presented to one eye and a pink noise mask to the other, both at the same spatial location, but with varying time durations of (8, 17, 33, 66, 133, 266, and 531 ms). A 2-up 1-down staircase was used to measure the contrast detection thresholds of the Gabor target at each duration.

Results: On average, suppression increases linearly as stimulus duration increases. This increase starts at a duration of 8 milliseconds until it reaches 133 milliseconds, at which point it plateaus, indicating suppression has reached saturation. This observed pattern aligns with the expectations derived from the literature review. In one of the participants, a decrease in threshold elevation at the 266-millisecond mark is detected suggesting that there may be individual differences in the dynamics of suppression.

Conclusion: Interocular suppression begins to build-up immediately upon visual detection of the presented stimulus. There is a positive linear correlation between suppression threshold elevation and stimulus duration such that suppression is lowest at brief durations, and increases with increasing stimulus duration, until a sufficiently large duration is reached, after which, suppression saturates. As such, the low levels of suppression obtain in the previous study can be attributed to the shorter duration of the stimuli used.

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16 - Circulating Lipid Profile Markers of Plaque Instability in Individuals with Severe Carotid Atherosclerosis

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Background: Cardiovascular disease remains the leading cause of death worldwide. Unstable carotid atherosclerotic plaques have been associated with a higher incidence of ischemic strokes. Atherosclerosis is the build-up of fatty deposits in the inner layer of arteries. Lipids, like cholesterol must be carried through the circulation in the form of lipoproteins: low-density lipoproteins (LDL) contain the apolipoprotein B (ApoB) on its surface, whereas high-density lipoproteins (HDL) contain the apolipoprotein A1 (ApoA1). Statins are drugs that inhibit an enzyme in the cholesterol biosynthesis pathway to reduce circulating cholesterol. Although the roles of lipoproteins, lipids and statins have been well-studied in the context of carotid atherosclerotic development, their association with atherosclerotic plaque instability currently remains unclear.

Objective: To investigate associations between serum lipid profiles, statin use and various grades of plaque instability.

Material and Methods: Males and post-menopausal females receiving a carotid endarterectomy were recruited at the Jewish General Hospital and McGill University Health Center. Written informed consent was collected from all study participants. Patients' clinical history and medical information were obtained through a detailed questionnaire and electronic medical records. Fasted blood samples were collected before surgery and were used to measure serum lipid profiles (HDL, ApoA1, LDL, ApoB). Carotid plaques were obtained during surgery, stained with H&E, and their stability was blindly characterized by pathologists according to the American Heart Association classification by Stary et al., into four groups: (1) definitely stable, (2) probably stable, (3) probably unstable and (4) definitely unstable. Statistical analyses were conducted using SPSS software.

Results: The final analysis included 745 patients. When comparing circulating markers in groups (1) definitely stable (2) probably stable (3) probably unstable and (4) definitely unstable, LDL levels were significantly higher in group 3 compared to group 1 ($p=0.022$). When comparing circulating markers in groups Stable (comprised of groups 1 and 2) and Unstable (comprised of groups 3 and 4), both LDL and ApoB levels ($p=0.014$ and $p=0.038$, respectively) were significantly higher in the Unstable compared to the Stable group. Further associations were identified after stratifying patients into groups based on whether they were on statin therapy. For patients not on statin therapy, both HDL and ApoA1 levels ($p=0.050$ and $p=0.040$) were significantly lower in the Unstable compared to the Stable group. For patients on statin therapy, both LDL and ApoB levels ($p=0.017$ and $p=0.026$) were significantly higher in the Unstable compared to the Stable group.

Conclusion: Our findings demonstrate that there are significant associations between LDL, ApoB, HDL and ApoA1 levels and various grades of carotid atherosclerotic plaque instability, which may be used to predict the risk of stroke. Moreover, statin use may influence carotid atherosclerotic plaque instability.

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17 - Value and Appropriateness of Inpatient ANA Testing: A Clinical Audit

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Background: Systemic lupus erythematosus (SLE), a systemic autoimmune rheumatic disease (SARD), is characterized by dysregulation of the immune system, leading to inflammation and tissue damage. Early diagnosis of SLE and other SARDs is crucial for timely intervention and management. Screening for antinuclear antibodies (ANA) is commonly used to help diagnose SLE and other SARDs. However, a positive ANA test lacks specificity, and testing when a diagnosis of SLE or other SARD is unlikely can lead to false positive results, with consequences for patients and the healthcare system. A significant number of ANA tests are ordered among hospitalized patients at the McGill University Health Centre (MUHC) each year, and it is unknown what proportion of these have appropriate indications for ANA screening. To address this, our project aims to assess the proportion of inpatient ANA testing deemed appropriate based on Choosing Wisely® Canada recommendations.

Methods: We are performing a retrospective chart audit, sampling 50 patients at random who had an ANA test result from June to October 2023 during a hospitalization at the MUHC. Patient sex, age, ordering physician specialty, ANA test result (titre[s] and pattern[s] if the test was positive), and hospitalization details (including length of inpatient stay) were collected from electronic medical records. We used descriptive statistics to summarize ANA test results and patient characteristics.

Results: Of the 20 inpatient charts reviewed to date, 7 (35.0%) were female, with a mean age of 59.3 (Standard Deviation, SD 25.7) years at time of ANA testing. The mean length of inpatient stay was 41.3 (SD 88.8) days, and 3 patients (15.0%) died during hospitalization. ANA was positive in 13 (65.0%) at a titre of 1:80 or greater and positive in 12 (60.0%) at a titre of 1:160 or greater, with the most common pattern reported at highest titre being homogenous. Mean turnaround time for ANA results was 84.2 (SD 20.3) days. Of the ANA tests ordered, most were ordered by cardiologists (25%) or general internists (20%), and 5% were ordered by rheumatologists. Six (30%) had a **prior** ANA ordered at MUHC (5 within the past year). Two other individuals had a second ANA test performed during the same hospitalization. We plan to further review patients' charts to identify clinical indications for ANA testing and assess the diagnostic value of ANA testing for diagnosing autoimmune conditions at MUHC.

Conclusions: In our sample, inpatients who undergo ANA testing at MUHC tend to have lengthy hospitalizations, which suggests they are clinically complex. Two-thirds of ANAs performed on inpatients returned positive, while the proportion with SARDs or specific autoimmune conditions is expected to be much lower. Furthermore, nearly a third had a previous ANA test ordered, most in the prior year. Our quality improvement study will contribute to optimizing resource utilization by defining targets for appropriate ANA testing and repeat testing, ultimately improving patient outcomes through appropriate testing.

18 - Synthetic Double-stranded RNA Induces M2-like, Anti-Inflammatory Macrophage Phenotypes In Vitro

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Atopic asthma is characterized by heightened expression of Th2 cytokines: Interleukin-4 (IL-4), -5, -13 and immunoglobulin E, as well as the infiltration of Th2 CD4⁺ T cells and eosinophils in the lung. While the Th1/Th2 balance is understood to be a crucial factor in immune response, its role in mediating anti-viral and cytotoxic responses remains inadequately elucidated. Studies conducted on murine models of asthma have provided evidence that the induction of a Th1 response alleviates the pathology associated with Th2 responses. In contrast, the suppression of Th1 cytokine-related signaling has been found to yield the inverse outcome. The identification of viral infections as contributors to asthma exacerbations, along with the observed Th1 immunopathology in specific severe asthma endotypes, suggests that a Th1 response may play a role in disease pathology. To study the role of the induction of a concomitant Th1 immune response we took advantage of Poly I:C (PIC), a synthetic double stranded RNA polynucleotide that can mimic viral RNA. PIC triggers various pathogen recognition receptors, leading to the production of interferons and other inflammatory cytokines associated with Th1 response and consistent with antiviral response. Following the preliminary data of Sun et al (2024) showing an inhibition of the immune response to allergen challenge by PIC and mediated by macrophages *in vivo*, this study aimed to examine the modulation of murine bone marrow derived macrophages (BMDMs) *in vitro* following PIC treatment. To do this bone marrow was extracted from the limb long bones from naive female BALB/c mice (8-13 weeks old). Hematopoietic stem cells were cultured in DMEM containing Macrophage Colony Stimulating Factor (M-CSF) on day 0, then treated with recombinant mouse interleukins (IL-4, IFN- γ) on Day 7 and Poly I:C on Day 9. Real-time RT-quantitative PCR (RT-qPCR) was conducted after harvesting of BMDMs 6 hours and 24 hours post PIC treatment. Preliminary results demonstrate that cells cultured with IFN γ and IL-4 resulted in M1 and M2 macrophage phenotypes, with increased expression of iNOS and arginase (Arg)-1, respectively. Six hours post-PIC treatment, IL-4 treated cells have heightened expression of Toll-like receptor (TLR3), tumour necrosis factor (TNF) α , and IFN β . The current data suggest that TLR3, a double-stranded RNA receptor, exhibits a larger upregulation in the presence of a viral mimic in M2 polarized macrophage phenotypes, than in M1 polarized macrophages. Furthermore, the presence of PIC leads to increased expression of anti-inflammatory cytokines (IL-10 and Arg-1), which is consistent with the observed anti-inflammatory response in the OVA-asthma model. Further data collection will be collected at 6 and 24 hours to determine the kinetics of Th1/Th2 balance in the murine OVA-asthma model. Our results currently show that viral triggers may provide a protective effect by favoring the M2 macrophage phenotype, which, in turn, generates a more anti-inflammatory disease environment. By understanding these complex interactions, we may identify novel pharmaceutical approaches that target not only asthma pathologies, but a broad range of Th2-mediated inflammatory disorders.

19 - Targeting O-GlcNAc Transferase with small molecule inhibitors in human leiomyosarcoma cell lines

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Introduction: Soft-tissue sarcomas (STS) are tumors of mesenchymal origin that represent 1% of adult cancers. Leiomyosarcoma (LMS), a malignant tumor type originating from smooth muscle cells, represents 10-20% of sarcomas. The standard of care for LMS is surgical intervention supplemented with chemotherapy (mostly doxorubicin) or radiotherapy. The response rate to doxorubicin is only 16-27% of patients with advanced sarcoma, emphasizing the need for novel therapeutics. Recent advances in metabolomics highlight the involvement of the hexosamine biosynthesis pathway (HBP) in tumor progression in several cancer types. HBP leads to the formation of UDP-GlcNAc precursor required for glycosylation of proteins. The addition of glycosidic residues can affect the function of key actors in cancer progression, including oncogenes, tumor suppressor genes, transcription factors, and kinases. Our group previously demonstrated that high expression of GFPT2, the rate-limiting enzyme in HBP, is associated with poor outcomes in uterine LMS. Next, we aim to evaluate whether targeting O-GlcNAc transferase (OGT), the downstream enzyme of HBP, can impede LMS growth. OGT catalyzes the addition of O-GlcNAc residues to proteins in a process called O-GlcNAcylation, the most abundant type of glycosylation. Our preliminary results have shown that the OGT gene is highly expressed in sarcoma. In this study, we sought to evaluate the effect of OGT inhibitors on the viability of LMS cell lines derived from primary and metastatic LMS.

Material and Methods: Three human LMS cell lines (derived in the laboratory of Dr. Jonathan A. Fletcher, Harvard Medical School) were used in this study. LMS03 was derived from diaphragmatic metastasis of soft-tissue LMS (male patient), LMS04 from retroperitoneal metastasis of uterine LMS (female patient), and LMS05 from primary thigh LMS (male patient). LMS cells were seeded in 96-well white plates at 25,000 cells per well for 24 hours prior to 24-hour treatment with different concentrations of OGT inhibitors: OSMI-1 (MCE), OSMI-4 (MCE), ST045849 (Sigma). Next, OGT inhibitor treatment was compared or combined with doxorubicin (MCE). Cell viability was assessed using Cell Titer-Glo (Promega).

Results: OSMI-1 decreased cell viability in all three LMS cell lines with a dose-dependent response. Maximum effect was reached at 100µM for 24 hours. OSMI-4 induced dose-dependent response only in LMS05, though to a lesser extent than OSMI-1. ST045849 decreased cell viability in all cell lines after 24 hours of treatment with dosage at 5µM in LMS03 and 100µM in LMS04 and LMS05. Only LMS05 was sensitive to doxorubicin treatment. OSMI-1 and OSMI-4 produced a synergistic effect with doxorubicin only in LMS05. Potential synergistic effects with ST045849 are yet to be evaluated.

Conclusions: OGT inhibitors decreased cell viability and either improved or outperformed doxorubicin efficacy in LMS cell lines. Future studies will evaluate BADGP as an additional OGT inhibitor and combined treatment with other chemotherapies. Exploring how OGT inhibition modulates the function of O-GlcNAcylated proteins can lead to a better understanding of the therapeutic potential of targeting HBP in LMS.

Source of Funding: This work was supported by the Leiomyosarcoma Direct Research Foundation (LMSDR) and by the Fulbright Canada-Mitacs Globalink program.

20 - Sex Differences in the Impact of Extreme Heat on Cardiovascular Disease Outcomes: A Systematic Review and Meta-Analysis

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Background: Numerous studies have demonstrated the association between extreme heat events and increased cardiovascular morbidity and mortality. However, sex-based differences in this association have not been fully investigated. Therefore, the objective of this study is to synthesize and analyse literature on cardiovascular disease (CVD) related morbidity and mortality during extreme heat periods, with a focus on investigating differences in outcomes between males and females.

Methods: Relevant studies were identified through comprehensive searches of the electronic databases PubMed, Embase, and Scopus, focusing on English articles published from 2004 to 2024. Inclusion criteria were observational studies using ecological time series, case crossover, or case series study designs that reported CVD outcomes related to heat exposure and analyzed results stratified by sex. Estimates of association between extreme heat and CVD outcomes for males and females were extracted by two reviewers using the Covidence software. Two major methods were considered to define extreme heat exposure: 1) frequency of extreme heat days, which focused on counting the number of days that meet a specific threshold for extreme heat; 2) incremental temperature increase, which examined the health impact of each degree increase in temperature. Quality of evidence and risk of bias were evaluated following the Navigation Guide Criteria methodology. We conducted a random effect meta-analysis of ratios of relative risks (RRR) between males and females for studies measuring incremental temperature increase. The presence of heterogeneous effects between subgroups were assessed by conducting Cochran Q tests. The study protocol was registered with PROSPERO (CRD42024547866).

Results: The search strategy led to 6126 articles, of which 316 articles were selected for full text screening, and then finally 91 studies for the systematic review and 64 studies for the meta-analysis. The identified studies were conducted across world, with a leading role of East Asia (both in terms of number of publications and of sample size), followed by Europe and North America. Source data spanned from 1985 to 2021. According to the meta-analysis, the female:male pooled RRR was 1.0049 (95% CI: 1.0023, 1.0075) for mortality, while 1.0020 (95% CI: 0.9954, 1.0086) for morbidity. These RRRs indicated that the relative risk for females is slightly higher than for males in the context of the association between heat and CVD related mortality, but not significant for morbidity. Significant heterogeneity was detected by I^2 (Mortality: $I^2 = 93.1\%$, $p < 0.0001$; Morbidity: $I^2 = 98.9\%$, $p < 0.0001$), suggesting substantial variability in the effect estimates across studies.

Conclusion: This review strengthens the evidence on the increase in CVD risk due to ambient heat exposures and reveals the underlying differences between males and females. The increased CVD mortality in females could be due to sex-specific effects across different regions and countries investigated. Therefore, further research is needed to characterize these differences on a regional scale.

Source of Funding: This study is supported by the Canadian Institutes of Health Research (CIHR), under Catalyst Grant: Supporting research on priorities outlined in Canada's Chief Public Health Officer (CPHO).

21 - Proof-of-principal for the novel mRNA-based cure of rare genetic disease Cystinosis

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Background: Cystinosis is a rare autosomal recessive disease caused by mutations in the gene encoding the transmembrane lysosomal cystine transporter cystinosin (CTNS). The absence of functional cystinosin causes excessive accumulation of cystine in lysosomes, leading to infantile nephropathic cystinosis. It appears in the first year of life causing poor growth and metabolic imbalances due to kidney proximal tubule dysfunction. These children suffer from many illnesses at a very young age including rickets, neuromuscular abnormalities, retinal defects, learning disabilities, and kidney function that declines rapidly leading to end stage renal disease often requiring transplantation or dialysis by their mid-teens. Current treatments involve oral cysteamine to reduce lysosomal cystine loads by bypassing the cystinosin channel. However, it fails to prevent the need for kidney transplantation nor does it address cystinosis complications in adulthood such as myopathy, encephalopathy, male infertility, coronary artery disease, and hypothyroidism. Furthermore, a subset of patients do not respond to this treatment. During the COVID-19 pandemic, Moderna's vaccines successfully demonstrated the ability to deliver and express exogenous mRNA in human tissues; we propose that a similar approach can be taken to treat cystinosis. In hopes to succeed where current treatments fail, we collaborate with Moderna to investigate an mRNA based cystinosin replacement treatment for cystinosis patients.

Methods: We will use cell culture techniques to grow a panel of CTNS mutant fibroblasts and proximal tubule kidney cells, harvested from cystinosis patients, and transfect into them mRNA encoding the cystinosin protein. We will use various molecular biology techniques to characterize the expression and stability of cystinosin generated from the exogenous mRNA. Finally, we will perform functional assays to assess the mRNA efficacy in reducing intra-lysosomal cystine levels.

Results: To study this, we selected and characterized a panel of control and CTNS mutant human fibroblasts and a panel of control and CTNS mutant human proximal tubule cells. We have submitted the mRNA sequence for the lysosomal isoform of cystinosin to Moderna and they have generated modified V5-tagged mRNA encoding cystinosin that ensure sustained high level translation of protein. To validate the proteins produced by Moderna's mRNAs, we performed western immunoblots against the V5 tag following transfection into control fibroblasts and proximal tubule cells and demonstrated their targeted expression to lysosomes using confocal microscopy. We are currently developing a novel quantitative colorimetric sodium-nitroprusside screening procedure to test the effectiveness of Moderna's mRNA on the abnormal accumulation of cystine in mutant cells. The planned experiments for this summer will focus on demonstration that the Moderna mRNA reduces intra-lysosomal cystine levels in cystinosis patient cells. Our goal is to establish proof of principle for a novel mRNA technology to cure this debilitating rare disease.

Conclusions: We believe that this mRNA-based approach has the potential to offer better outcomes for cystinosis patients, cure cystinosis, and further our understanding of mRNA applications in treatments.

Funding: This project is supported by the Cystinosis Research Foundation, RIMUHC Foundation, and the McGill Summer Research Bursary Program.

22 - Role of Caldesmon in Smooth Muscle Efficient Force Maintenance

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Introduction: There are three types of muscle in the body: skeletal muscle controls movement and posture, cardiac muscle pumps the blood, and smooth muscle (SM) is involved in many involuntary functions in all other hollow organs of the body. As for all muscle types, SM contraction is mediated by myosin molecular motors, that transform ATP's chemical energy into mechanical work, to pull on actin filaments.

Unlike other muscle types, SM can maintain force for long periods of time with low ATP consumption. This is a poorly understood phenomenon dubbed the latch-state. The actin regulatory protein, h-caldesmon (hCaD), may contribute to this state. Indeed, it has been shown that hCaD modulates the myosin-actin mechanical interactions and that its effects can be partially reversed by its phosphorylation (p-hCaD)¹. Ultimately, we want to investigate the role of hCaD in the latch-state but first, we must verify if we can reproduce the modulation of the myosin-actin mechanical interactions by hCaD in our assays. Thus, this project aimed to measure the effect of hCaD and p-hCaD on the molecular mechanics of actomyosin, using the in vitro motility assay (IVMA).

Methods: hCaD (1.1 μM) was phosphorylated by incubation with extracellular signal-regulated kinase (ERK) (0.45 μM) and ATP (1.2 mM) at 30°C for 90 minutes, and its phosphorylation will be confirmed with *phos-tag* SDS-PAGE.

For the IVMA, myosin molecules (0.2 μM) were randomly adhered to a nitrocellulose coated microscope coverslip of a flow through chamber. BSA (7.5 μM) was perfused to bind remaining locations on the surface of the chamber. Next, hCaD (0.4 μM) or p-hCaD (0.4 μM) was perfused to bind to myosin, followed by fluorescently labelled actin (0.04 μM). Perfusion of a viscous methylcellulose buffer favored the contact between myosin and actin, and ATP (1mM) in the buffer allowed the myosin to propel the actin under the regulation of hCaD or p-hCaD. The actin filament velocity (v_{avg}) was calculated using rapid time-stamped analysis² which tracks the displacement of individual filaments over time.

Results and Discussion: We found that v_{avg} of hCaD regulated actin (0.50 $\pm$ 0.04 $\mu\text{m/s}$, n=6) was significantly lower when compared to the v_{avg} of unregulated actin (0.66 $\pm$ 0.03 $\mu\text{m/s}$, n=7, $p < 0.0001$) and to the v_{avg} of p-hCaD regulated actin (0.59 $\pm$ 0.07 $\mu\text{m/s}$, n=4, $p = 0.02$). These results also show that phosphorylating hCaD reverses the actin regulation because there was no significant difference in v_{avg} between unregulated actin, and p-hCaD regulated actin ($p = 0.06$). This demonstrates that hCaD regulation reduces v_{avg} , and that this effect is mitigated by ERK phosphorylation of hCaD. Unlike previous research that described hCaD phosphorylation as partially reversing the effects of hCaD on actomyosin, we found that phosphorylation fully reverses the effects. Having verified the role of hCaD phosphorylation on actomyosin regulation, we will now investigate the latch-state by making molecular force measurements in the presence of hCaD and p-hCaD.

References:

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23 - Reading Efficiency in Amblyopia

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Amblyopia, more commonly known as “lazy eye”, is a condition where incoming information from one of the eyes is processed poorly. In the past it has been shown that reading is altered in amblyopia; individuals affected by this condition tend to have a slower reading speed and experience different eye movements when compared to controls. We believe that this dissimilarity may be accounted for by differences in brain oscillations of amblyopic participants. Thus, we will be using random temporal sampling in our experiment to evaluate this theory. In this study, we aim to investigate whether there are differences in the reading efficiency along the temporal sampling domain of controls and amblyopic individuals.

To quantify the reading efficiency of participants, we used the random temporal sampling technique at an accuracy level of 50%. This data was collected using a four-alternative forced-choice task. The target that we used was one of 800 three-to-six letter words. These 800 words were equally divided into four categories. On each trial, participants had to read one of these words to the best of their ability, as a varying level of noise impeded their reading, and they had to choose one of the four categories that the word belonged to.

Overall, we found that controls read more efficiently than amblyopic participants. Controls were most efficient in the binocular condition. Amblyopic participants were surprisingly most efficient at reading in the monocular amblyopic condition (when reading with their weak eye). Amblyopes struggled the most in the binocular condition.

In conclusion, it is clear that the reading patterns of controls and people with amblyopia differ in significant ways, and this may be partially explained by differences in their neural activity. Controls showed an overall better level of binocular summation, meanwhile amblyopes seemed like they were unable to combine binocular visual information to aid them in word identification.

24 - A bioinformatics approach to investigate emerging variants of Chikungunya virus from the 2020 Cambodia epidemic

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Background: Chikungunya virus (CHIKV) is a mosquito-borne virus that causes severe joint and muscle pain lasting for months to years. Since its discovery in 1952, CHIKV was mostly limited to sporadic outbreaks in Africa and southeast Asia until its emergence in a series of outbreaks from 2005-2007. One point mutation (A226V) in the E1 viral glycoprotein enhanced CHIKV transmission by *Aedes albopictus* mosquitoes and facilitated an expansion of the virus in urban settings. Protection against subsequent CHIKV infection is facilitated by neutralizing antibodies directed towards the viral entry and fusion proteins, respectively E2 and E1. Rising global temperatures have coincided with an increase in suitable habitats for CHIKV-carrying mosquitoes and naive individuals at risk of CHIKV infection. Understanding the molecular determinants of immune escape informs the development of diagnostics, therapies, and vaccines to mitigate the economic and public health burden of future epidemics.

Objective: Examine CHIKV genomic sequences from two consecutive outbreaks in Cambodia, in 2011 and 2020, for which poor cross-neutralization has been reported. We hypothesize that mutations within E1 and E2 of the 2020 CHIKV strain are responsible for poor neutralization activity of antibodies generated by memory B cells from the 2011 CHIKV outbreak.

Methods: We employed a comprehensive bioinformatics approach to analyze 146 CHIKV sequences from Cambodia from outbreaks in 2011 and 2020. A multiple sequence alignment using MUSCLE to obtain BAM files compared the Cambodian sequences with reference sequences such from the prototypical E1-A226V La Réunion epidemic strain (LR2006-OPY1) and an Asian genotype strain from 2011 (V0603310_KH11_BT). FreeBayes was used for variant annotation, and the effects of these variants were predicted using SnpEff. We focused on identifying key regions that distinguish the various Cambodian strains, determining the number of these regions, their coding status, associated proteins, and specific domains. Structural and functional impacts of the mutations were visualized using Jalview, with specific attention to E1 and E2 to understand their role in pathogenesis. Open Reading Frames (ORFs) were identified using reference annotations and coordinates. The entire process was run in parallel, combining MUSCLE alignments with FreeBayes for efficiency. Modules and job submissions were managed using the Compute Canada infrastructure, with relevant guides and modules referenced for software installations and usage. This approach allows us to map evolutionary changes, understand the unique features of the Cambodian sequences, and evaluate their potential impact on viral phenotype and pathogenicity.

Expected Results: We anticipate to find point mutations in E1 or E2 that are shared by multiple isolates within our cohort of 2020 Cambodian sequences. These mutations will inform functional studies that will test our hypothesis through *in vitro* plaque reduction neutralization tests and *in vivo* mouse models of infection.

Conclusions: Emerging CHIKV variants in Cambodia are expected to exhibit mutations that can potentially enhance viral spread and alter immune recognition. These findings underscore the importance of continuous genomic surveillance of emerging and emerged viruses. Our study aims to provide novel insights into the molecular mechanisms driving CHIKV evolution and highlights the critical role of bioinformatics in infectious disease research.

25 – Dietary Risk Factors for Coronary Artery Disease: a UK Biobank Study

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Background: Coronary artery disease (CAD) is the most common type of heart disease, as it affects approximately 5% of the world population causing an estimated 1 in 4 deaths. This condition is characterized by the reduction of blood flow to the heart due to the blockage of the coronary arteries, thus increasing the occurrence of heart attacks. Many dietary elements can be identified as risk factors. Nutrition plays an important role in cardiovascular health, and the assessment of certain dietary components and their impact on CAD can inform risk stratification.

Methods: In this study, we included UK Biobank participants of European descent that had never taken lipid lowering cholesterol medication in the past ($n = 392,853$). To identify the effect of specific dietary intakes on CAD, we used logistic models adjusted for age, sex, body mass index (BMI), systolic blood pressure (SBP), blood pressure medication intake, smoking, apolipoprotein B (ApoB) and diabetes. The associations of fish intake, meat intake, red meat intake, salt intake, fruit and vegetable intake were examined.

Results: The mean age was 56 years old (55.8 ± 8.0 years), and the population was mostly composed of men (55.8% males). In the fully adjusted model, vegetables, fruits, and fish intake have been observed to decrease CAD risk (OR = 0.831 and $P = 5.91 \cdot 10^{-18}$, OR = 0.875 and $P = 1.06 \cdot 10^{-18}$, OR = 0.933 and $P = 8.35 \cdot 10^{-5}$, respectively). More specifically, oily fish intake has shown better results for lowering the risks of CAD than non-oily fish (OR = 0.929 and $P = 4.58 \cdot 10^{-7}$, OR = 0.965 and $P = 1.97 \cdot 10^{-2}$, respectively). However, meat and salt intake were associated with increased CAD risk (OR = 1.25 and $P = 2.03 \cdot 10^{-6}$, OR = 1.14 and $P = 1.61 \cdot 10^{-20}$, respectively). We also observed that red meat – variable excluding poultry – also increased risks in CAD (OR = 1.14 and $P = 1.22 \cdot 10^{-3}$).

Conclusion: Our results suggest that diet has a strong influence on CAD, as some factors increase risk (salt, red/non-red meat) and some decrease risks (vegetables, fruits, and oily/non-oily fish). In the future, the effect on a wider variety of cardiovascular diseases will be assessed.

26 – Prevalence and Correlates of Mental Health Problems in Young (Birth-5 Years) Children across Africa: A Literature Review

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Background: Mental health problems are the leading cause of disability-adjusted life years in children and a barrier to reaching their full developmental potential. Understanding the burden of mental health problems among children and accompanying risk and protective factors is critical to developing and implementing interventions to promote mental health. The objective of this literature review was to summarize existing studies on the prevalence and correlates of mental health problems in young children across Africa and to identify gaps and future directions for research.

Methods: In an ongoing review that began June 17th, we searched the following databases MEDLINE, Global Health (OVID), Scopus, PsycINFO, CINAHL, and Web of Science. Inclusion criteria were a focus on children between birth and five years old in Africa (population), exposure to family-level risk or protective factors for children's mental health (intervention), and children's positive mental health or mental health problems (outcome). Results were imported into *Covidence*. Articles were screened by title and abstract, followed by a full-text review of retained articles. Articles were excluded if outcomes and study population did not fit the inclusion criteria.

Results: Of the 983 articles identified so far, 258 duplicates were removed. The remaining 725 articles underwent title and abstract screening, where 623 articles were excluded. After a full-text review of 102 articles, an additional 73 articles were excluded. Twenty-nine articles were retained for the review. Articles were published between 2000 and 2024 and consisted of longitudinal studies (n=7), cross-sectional studies (n=18), editorials (n=2), scoping reviews (n=1), and randomized control trial analyses (n=1). Articles spanned 35 African countries, with sample sizes between n=16 to n=92,433. The most represented country was South Africa (n=14). Areas of interest were maternal mental health, socioeconomic status and parental education status as predictors of child mental health outcomes, and the psychometric accuracy of current screening tools. In preschool-aged children, prevalence rates for mental health problems (e.g. externalizing problems and delayed socioemotional development) ranged from 4.3-51.0%. Generally, boys were more likely to experience externalizing problems (between 9.7-42.0%), such as hyperactivity and behavioral issues. Girls had higher prevalence rates of internalizing symptoms, for example, anxiety (between 10.0-29.7%). Studies found that maternal depression, having unemployed parents or parents that did not complete secondary school, low socioeconomic status (defined as being in the two lowest quintiles of household wealth), and housing insecurity were associated with a higher prevalence of both anxiety and behavioral problems in children.

Conclusion: Prevalence rates of mental health problems across preschool-aged children in Africa varied across countries. However, certain parental and household characteristics were consistently associated with mental health outcomes. Significant gaps in the literature on child mental health in Africa include most data coming from a small handful of countries, a lack of studies on children's positive mental health outcomes and little examination of the impact of paternal characteristics and involvement on children's mental health.

Source of Funding: The literature review was supported by the Dr. Alice Benjamin Global Maternal and Child Health Fund Award through the McGill Global Health Scholars – Undergraduate Program.

27 – Exploring FDA-Approved Drugs for Sensitizing Chemotherapy-Resistant Cancer Cells: Establishing Dose-Response Baselines for Methotrexate, Etoposide, and Topotecan

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Introduction: Chemotherapy resistance remains a significant challenge in cancer treatment; therefore, there is a critical need for strategies to enhance drug efficacy. Here, we investigate the potential of existing FDA-approved agents to sensitize cancer cells resistant to standard chemotherapy. We hypothesize that these drugs can improve the response of resistant cancer cells to treatment. We aim to establish baseline dose-response curves in two colorectal cancer cell lines (COLO320 DM and HSR)—using methotrexate, etoposide, and topotecan. These are isogenic cell lines; however, DM is known to be more resistant to many standard care drugs compared to HSR. Previous publications attributed this difference to the presence of double minutes in the DM. As Next Generation Sequencing was already applied to these cell lines, differences in their response to drugs can be easily mapped to genomic differences.

COLO320 DM cell line contains double minutes as additional genetic material and was reported to become quickly resistant to methotrexate treatment. Topoisomerases are important for DNA maintenance, and we would like to test whether their inhibitors can re-sensitize them to chemo. To study that, we need to establish a baseline response to test if these two cell lines indeed respond to individual drugs with measurable differences in sensitivity, which will provide a reference for future evaluation of drug combinations aiming to enhance treatment efficacy.

Material and Methods: The cell lines were cultured under standard conditions in appropriate growth media (RPMI-1640), supplemented with 10% fetal bovine serum and 1% penicillin-streptomycin, and maintained at 37°C with 5% CO₂. MTX, etoposide, and topotecan stock solutions were prepared in dimethyl sulfoxide and stored at -20°C. Nine serial dilutions of each drug were stored to achieve final concentrations ranging from 1x 10⁻⁷ µM to 100 µM for each drug in a 96-well.

Cells were seeded in 96-well plates at 10,000 cells per well and allowed to adhere overnight. Following, the cells were treated with the nine previously obtained drug dilutions with technical repeats. Luminescence-based cell viability assays (CellTiter-Glo®, Promega) were performed 72 hours post-treatment using a plate reader, and the data were normalized to the untreated control wells. Dose-response was generated and analyzed for each drug using Excel.

Results: The results demonstrate distinct sensitivity profiles between the cell lines to methotrexate, etoposide, and topotecan. The DM cells exhibited higher EC₅₀ values for methotrexate compared to HSR cells confirming their reported resistance to this drug. Interestingly, both etoposide and topotecan showed differential effects on the two cell lines. DM cells displayed a higher EC₅₀ for etoposide compared to HSR while topotecan treatment resulted in a lower EC₅₀ in DM cells. These findings suggest that the presence of double minutes in DM cells not only confers resistance to methotrexate but also alters sensitivity to topoisomerase inhibitors.

Conclusions: Our study establishes baseline sensitivity profiles for COLO320 DM and HSR cell lines to methotrexate, etoposide, and topotecan, highlighting distinct drug responses linked to double minutes. These findings exhibit chemoresistance mechanisms in colorectal cancer and suggest strategies to overcome drug resistance.

28 – Assessment of Optimal Inhaler Therapy Strategies in the Management of Acute Exacerbations of COPD (AECOPDs) using Oscillometry: A Cross-Sectional Study

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Introduction: Chronic obstructive pulmonary disease (COPD) is a common lung condition characterized by shortness of breath, exercise intolerance, and sudden ‘lung attack’ episodes known as acute exacerbations of COPD (AECOPD) or ‘exacerbations.’ Exacerbations involve inflammation in the airways, limiting airflow, especially during expiration. Long-acting bronchodilators (LABDs) are used daily for chronic COPD treatment, while short-acting bronchodilators (SABDs) are typically used during exacerbations. However, there is currently no standard approach to which inhaler types are used during an exacerbation. There is a lack of evidence regarding whether LABDs should be continued, or withheld, while SABDs are prescribed during the exacerbation. **Oscillometry**, a non-invasive method of measuring the resistance in the airways and the limitation to airflow in the lungs, measures lung function during relaxed breathing and detects subtle changes before and after inhaler doses, making it useful during exacerbations. The primary objective of this study is to assess the effectiveness of treating exacerbations with SABDs compared to a combination of long-acting and short-acting inhalers in patients with COPD who are experiencing and receiving treatment for an exacerbation. Secondary objectives include comparing the magnitude of difference in patient-reported dyspnea scores before and after the use of SABDs alone and with the use of both SABDs and LABDs and collecting information on side effects associated with the use of combined short- and long-acting therapies. We hypothesize that combined short- and long-acting therapies during exacerbations will improve lung mechanical properties and symptom scores, with an acceptable side effect profile compared to short-acting therapies alone.

Material and Methods: This cross-sectional study will use a convenience sampling approach to enlist 43 adult patients with COPD undergoing treatment for an AECOPD with both short- and long-acting inhalers. Patients will undergo three sets of oscillometry measurements: 1) at “baseline” (no inhaler), 2) after the SABD, and 3) after the LABD, following the SABD dose. Patients will also rate their shortness of breath (dyspnea) using a Visual Analog Scale (VAS) at baseline and after each inhaler administration. A post-AECOPD treatment and hospitalization chart review will gather information on potential side effects linked to combined short- and long-acting inhaler usage.

Results: The co-primary outcome variables are markers of expiratory flow limitation (reactance-volume loop area [AXV] and the mean inspiratory minus expiratory total respiratory system reactance [mean ΔXrs]). The secondary outcome variables are changes in VAS dyspnea scores between each set of inhaler administrations as well as the standard parameters obtained by spectral oscillometry. Differences between each set of measurements will be compared by repeated measures ANOVA.

Conclusions: This study aims to provide guidance on the best treatment approach for AECOPDs. If oscillometry markers of expiratory flow limitation significantly improve with the addition of LABDs following SABDs, it would imply that patients are sub-maximally bronchodilated when using short-acting therapy alone.

Source of Funding: Funding is provided by the McGill University Health Centre (MUHC) Department of Medicine Contract Academic Staff (CAS) Research Award.

29 - Potential withdrawal effect of the 5-HT receptor agonist psilocybin in rats

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Background: Psychedelic substances, particularly psilocybin, are currently under investigation in clinical trials for their potential therapeutic effects for neuropsychiatry disorders such as depression, anxiety, and PTSD. Nevertheless, the FDA has recently raised concerns about the addiction liability of psychedelics due to the limited understanding of this potential danger. For this, our objective is to investigate the potential behavioral and synaptic changes induced by psilocybin during withdrawal.

Methods: Sprague-Dawley rats weighing 200-250 g (n=10) were randomly assigned to receive either vehicle (saline 0.9% i.p.) or psilocybin (10 mg/kg i.p.) for 7 consecutive days. On days 1, 7 (the first and last day of administration), 8, and 9 (24 and 48 hours post-administration), animals were placed in a clean home cage box, and behavior was observed and quantified for 10 minutes. RM Two-Way ANOVA was performed on these observations. On days 8 and 9, an open field test (OFT) was conducted to assess the anxiolytic response. Subsequently, rats were anesthetized with chloral hydrate (400 mg/kg, i.p.), and *in vivo* single-unit electrophysiology recordings were performed in dopaminergic and non-dopaminergic neurons from the Ventral Tegmental Area (VTA). T-tests were performed to compare both groups.

Results: No differences in body weight between the two groups were detected ($p > 0.05$). Similarly, RM Two-Way ANOVA found no differences in stereotypic behaviors (head twitch, grooming, dog shaking, and body licking) and non-stereotypic behaviors (defecation and rearing) on days 1, 7, 8, and 9. However, unpaired t-test analysis on day 9 (48 hours after the last administration) revealed that psilocybin induced an increase in grooming behavior compared to the control group ($p < 0.05$). Pearson correlation analysis showed a moderate correlation ($r = 0.640$; $p < 0.05$) between grooming and psilocybin administration on day 9. Additionally, the chord diagram indicated that restriction of psilocybin after repeated administration increased the number of positive correlations among all behaviors, suggesting a possible withdrawal effect induced by psilocybin in rats. On the other hand, OFT analysis showed no difference in locomotor activity and anxiety response between groups ($p > 0.05$). Similarly, we found no differences in firing activity of dopaminergic and non-dopaminergic neurons in the VTA (t-test analysis, $p > 0.05$). However, dopaminergic neurons became silent in the psilocybin group compared to vehicle-treated rats (vehicle = 21.21% vs. psilocybin = 3.03%), suggesting that this may be the mechanism by which psilocybin acts during withdrawal.

Conclusions: Repeated administration of psilocybin for 7 days shows a trend of increased behavior indicative of withdrawal symptoms. It also demonstrates that psilocybin induces neuronal changes in dopaminergic neurons after repeated administration. This highlights the importance of investigating the synaptic and behavioral changes induced by psilocybin during withdrawal. The findings from this research will contribute to the development of safer therapeutic protocols for using psychedelics to treat psychiatric disorders by improving our understanding of the balance between therapeutic benefits and addiction risks.

Source of Funding: CAPES-PrInt and PBEEE-FRQ

30 - Investigating the Protein-Protein Interactions of Slit Diaphragm Protein Crb2

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Background: Nephrotic syndrome, a disorder characterized by heavy proteinuria, arises when the glomerular filtration barrier is impaired. Podocytes are specialized epithelial cells responsible for maintaining integrity of the filtration barrier, and with dramatic morphological changes known as “foot process effacement”, the permselectivity of the filtration barrier is diminished. Crb2, a protein located in the slit diaphragm of podocytes, has been identified as a potential target for autoantibodies associated with nephrotic syndrome. However, the downstream effects of antibody interaction with Crb2 remain unclear. It is hypothesized that Crb2 signalling may contribute to cytoskeletal rearrangement, resulting in podocyte foot process effacement, slit diaphragm damage, and proteinuria. Given Crb2's intracellular motifs related to cytoskeleton interaction (FERM-binding and PDZ-binding), it is likely involved in maintaining cytoskeletal dynamics and slit diaphragm integrity. To explore the signalling pathways downstream of Crb2, our lab employed proximity-dependent biotinylation and proteomics (BioID). An examination of the functions and interactions of candidate proteins with Crb2 will provide insight into its signalling pathways, regulation of podocyte structure, and involvement in the pathology of nephrotic syndrome.

Methods: The interaction between Crb2 and the following proteins identified by BioID were evaluated: EphA2, Scrib1, 4.1G(EPB41L2), and FERMT2. Tagged constructs of these proteins were previously prepared and co-immunoprecipitation in HEK293 cells was employed to confirm interaction with Crb2. Full-length Crb2 and Tac-Crb2 (intracellular domain) were used to investigate Crb2 structure's role in its interactions. Upon confirmation of an interaction, deletion or mutation of the assumed binding motifs of Crb2 were generated and evaluated by Co-IP again. Additionally, intracellular localization of proteins of interest was evaluated in human podocytes by immunofluorescence, as well as their potential co-localization with Crb2.

Results: A conserved PDZ-binding motif in the C-terminus of full-length Crb2 allows binding to Scrib1—a membrane protein associated with cell migration, polarity, and proliferation—in HEK293 cells by co-immunoprecipitation. EphA2—a receptor tyrosine kinase involved in cell migration, adhesion, and proliferation—was also found to interact with full-length Crb2 and Tac-Crb2 (intracellular domain) in HEK293 cells. However, EPB41L2 and FERMT2, which are adaptor and scaffold proteins involved in cell adhesion and cytoskeleton dynamics, did not interact with full-length nor Tac-Crb2 by co-immunoprecipitation. Despite the presence of 4.1-ezrin-radixin-moesin (FERM) domains in both proteins, and a FERM domain-binding motif in Crb2, the interaction detected by BioID may be transient and irreproducible in this model.

Conclusions: The results demonstrate the potential participation of Crb2 in cellular signalling pathways that regulate cytoskeletal architecture in podocytes. Disruptions in these pathways, caused by Crb2 autoantibody binding, may lead to foot process effacement, slit diaphragm damage, and proteinuria, contributing to the pathology of nephrotic syndrome. With further research into the downstream activity of Crb2, the importance of cytoskeleton regulation can provide insights into and potential therapeutic targets for nephrotic syndrome.

31 - Overexpression of Zfh2 disturbs glial cell morphology in *Drosophila*

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Introduction: Glial cells function in various important roles within the developing and mature central nervous system (CNS). For example, glial cells contribute to the proper differentiation and patterning of neurons, and they regulate behaviors such as movement. The insect *Drosophila melanogaster* is an advanced genetic model system that is well suited to the study of glia. In the *Drosophila* CNS, our lab studies three main types of glial cells - astrocytes, ensheathing glia and cortex glia - which interact with neurons and exhibit similar functions to mammalian glia. Using RNA-interference (RNAi) for loss-of-function screening, we previously identified Zinc finger homeodomain 2 (Zfh2) as a glial regulator of motor behavior. Loss of Zfh2 from ensheathing glia led to a) deficits in adult climbing, and b) changes in glial morphology suggesting increased cell growth. Intriguingly, mutations in the vertebrate orthologs of Zfh2 (ZFHX3/ZFHX4) have been associated with motor defects, epilepsy and intellectual disability. To complement our understanding of the effects of reduced Zfh2 expression, here we explored the impact of Zfh2 overexpression on climbing ability and ensheathing glia morphology.

Material and Methods: Ensheathing glia were selectively targeted using the GAL4-UAS system. To achieve ensheathing glia-specific Zfh2 overexpression, we used R83E12-GAL4 to drive a UAS-Zfh2-mCherry transgene. Climbing ability was assayed by transferring flies to an empty tube, tapping them to the ground and calculating the proportion of flies that climbed vertically past a 6 cm threshold within five seconds. To examine the effects of Zfh2 overexpression on the morphology of ensheathing glia, we used immunohistochemistry to study the plasma membrane tethered reporter UAS-mCD8-GFP. Brains were dissected from adults in ice-cold PBS, fixed in 3.7% FA + 0.5% Triton X-100, washed in 0.5% phosphate buffered saline + 0.5% Triton X-100, then mounted on slides for imaging with confocal microscopy. Images were obtained using an Olympus FV1000 laser scanning confocal microscope and visualized using FIJI software.

Results: Upon overexpression of Zfh2, the membranes of ensheathing glia appeared thinner compared to controls, suggesting reduced growth and/or developmental defects. Interestingly, this contrasts with the effect of Zfh2 knockdown, which resulted in thicker membranes. Zfh2 overexpression in ensheathing glia did not affect adult climbing behavior, suggesting that the ability of ensheathing glia to regulate motor behavior is not sensitive to increased Zfh2 levels.

Conclusions and Future Directions: Our results support the idea that Zfh2 plays a role in regulating the growth and/or development of ensheathing glia. Further research will focus on extending our current data set and clarifying the link between Zfh2 overexpression and ensheathing glial morphology. In addition, we will explore whether increased Zfh2 levels lead to glial morphology defects at an earlier stage by examining third instar larvae.

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32 - Evaluation of Psych Corps Ghana's Psychological First-Aid Training

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Background: Ghana, a country in West Africa, faces challenges in providing access to mental health services due to the scarcity of mental health professionals in the country and to the insufficient funds put towards providing mental health services. Psych Corps Ghana is a non-governmental organization established to increase access to psychological care through the training of psychology graduates (referred to as psychologist assistants) who are then placed with mental health professionals during their obligatory national service. In this study, we aimed to determine the perceived effectiveness of the Psych Corps program by using qualitative research to examine its perceived impact on the professional skills of psychological assistants and the communities that they work with.

Methods: This study consisted of qualitative in-depth interviews (IDIs) and focus group discussions (FGDs) conducted in person at the Department of Psychiatry in the Korle Bu Teaching Hospital and Ghana Health Service hospital sites in the Greater Accra Region, as well as virtually with participants who could not meet interviewers in person. Data were collected from a sample of 40 adults (≥ 18 years) including current and former psychologist assistants (PA), members of Psych Corps Ghana's leadership (PCL), co-workers (CW) and, supervisors (SP) of PA during their national service, and community members (CM). The interviews were conducted by a trained MSc Public Health student (Chanelle Lawson-Lartego) and the study PI (Dr. Marilyn N. Ahun). Data are being analyzed using thematic content analysis, and as of now 11 transcripts have been analyzed.

Results: The 11 transcripts analyzed were from 4 PCLs (2 females, 2 males; 35-40 years old), 3 PAs (2 females, 1 male; 23-30 years old), 1 CW (male, 31 years old) and 3 SPs (1 female, 2 males; 30-60 years old). According to PAs the Psych Corps training teaches them how to put into practice their theoretical knowledge on mental health gained through their degree. This practical training equips them to provide psychological first aid. According to PCLs, the training has the positive impact of motivating trainees to pursue a career in mental health or to start an initiative to promote mental health after their national service. According to SPs, PAs are useful as they help reduce the burden on supervisors by assisting in the screening and evaluation of patients and addressing mental health-related stigma through community outreach activities. Lastly, PAs believe that they are useful as well because patients benefit from their provision of psychological first-aid while waiting to see a mental health professional.

Conclusion: Preliminary findings indicate that Psych Corps Ghana's training plays an important role in providing graduates with essential skills for their national service that they could not acquire from their psychology degree. These findings also suggest that the training contributes to increasing the number of mental health professionals in the country and making mental health services more readily available. Continued analysis of the data will shed more light on the perceived strengths and weaknesses of the Psych Corps program and identify potential avenues for improvement.

33 - Proteomic Profiling of Dorsal Root Ganglion in Mouse Model of Polytrauma with Spinal Cord Injury-associated Neurogenic Heterotopic Ossification

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Background: Neurogenic heterotopic ossification (NHO) is a major complication that follows spinal cord injury (SCI), leading to an abnormal formation of bone in soft tissues near big joints. Symptoms of NHO include joint pain and stiffness, impeding the rehabilitation process. Current treatment approaches for NHO such as radiation therapy and anti-inflammatory drugs are ineffective due to the lack of understanding of the underlying mechanisms. We hypothesize that the neuroinflammatory peptides released by the sensory neurons at Dorsal Root Ganglions (DRGs) into the musculotendinous tissue cause abnormal osteoblastic differentiation and mineral deposition.

Method: Three-month-old female C57BL/6 mice were anesthetized to induce SCI by transecting the spinal cord at the T9-T10 level. A musculotendinous injury (MTI) was generated in the left hindlimb by crushing the quadriceps muscle by surgical clamp for 15 seconds followed by a 2mm-tenotomy performed at quadriceps tendon, while the right limbs remained intact as internal controls. Subset of mice were euthanized at post-surgery Day 1 and Day 6. Proteins were extracted from the lumbosacral DRGs below the level of SCI and muscle cells from the quadriceps, quantified using Pierce™ BCA Protein Assay Kit, and analyzed using mass spectrometry to generate proteomics data sets. Scaffold 5 was employed for protein analysis, while pathway analysis was conducted using ShinyGo 0.80 and functional annotation was performed using David informatics.

Results: The preliminary results from the proteomics analysis reveal a noticeable upregulation in the expression of proteins linked to inflammation and immune response in the DRG on Day 6 compared to Day 1, indicating a state of neuroinflammation. Particularly, there was a significant increase in proteins associated with macrophages and neutrophils, as well as the activation of a pro-inflammatory reaction. Furthermore, proteins responsible for regulating calcium levels displayed pronounced expression patterns in the DRG, which play a role in supplying calcium ions for the mineral deposition process involving calcium phosphate. Further investigation will explore the potential involvement of neuropeptides associated with these proteins and to elucidate pathways connecting neuroinflammation to neurogenic heterotopic ossification. Western blot analysis will be used to validate the findings.

Conclusion: There was an increase in the expression levels of proteins associated with immunity, inflammation, and calcium regulation in the sensory neurons at DRG. Identification of specific proteins and their associated counterparts can show promise in developing safe and effective therapeutics for the NHO.

34 - Regulatory Challenges in Canada for Meal Replacement Products for Diabetes Remission

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Introduction: Two major clinical trials, DiRECT (UK) and DiaDEM (Qatar) demonstrated that a period of low calorie total meal replacement could induce type 2 diabetes remission in adults with this condition for 6 years or less, not requiring insulin therapy. These studies catalyzed Diabetes Canada's 2022 remission guidelines. However, Canadians do not have access to either the Cambridge Meal Plan used in these trials nor to a wide range of products from OptiFast (Nestlé Health Science). This is related to Canadian regulations on compositional and energy requirements for total meal replacement, which differ from those of the US, UK, and other jurisdictions. We are evaluating the nature and evidence for these differences. The overarching aim is to address barriers that impede Canadians from accessing potentially useful tools to achieve diabetes remission.

Materials and Methods: We are searching Health Canada and Government of Canada websites to identify the regulatory frameworks addressing total meal replacement in Canada. We are conducting similar searches for the US, and the UK, through the Food and Drug Administration (FDA) and the Commission Regulation (EU)/Food Standards Agency (FSA), respectively. We will tabulate key requirements, comparing jurisdictions, and assess the evidence that underpins these, where available.

Preliminary results: Meal replacement products used for total meal replacement in Canada need to meet specific nutritional compositions and follow Division 24 of the Food and Drug Regulations. Some appear to be outdated and contain unnecessarily strict labeling requirements. These include, but are not limited to, mandatory nutrient composition, daily calorie targets, minimum protein and fat content, and specific vitamin and mineral requirements.

Conclusions: The regulatory discrepancies between Canada and other jurisdictions that block access to a wider range of meal replacement products may be outdated and disadvantages many consumers who are on weight-loss diets. Addressing these challenges could involve updating Canadian regulatory frameworks to align with current international nutritional recommendations.

Sources of Funding: None

35 – Cross-Sectional Laboratory and Imaging Correlates of Valvular Disorders: A Study from the Courtois Cardiovascular Signature Program

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Introduction: Valvular diseases occur when one or more of the valves do not open or close properly. Heart valve disease (HVD) is a growing healthcare concern fueled by an ageing population, estimated to affect 1.5 million people in Canada over the age of 65 by the year 2040 (1). HVD is diagnosed using echocardiography as well as cardiac MRI. Blood markers such as C-reactive protein (CRP), the lipid marker lipoprotein(a) (Lp(a)) and Apolipoprotein(b) (Apo(b)) have been correlated to increased risk of cardiovascular disease and may have prognostic value for HVD (2). Functional changes in the heart's systolic and diastolic function have shown prognostic value for heart failure (HF) and could provide value to HVD prognosis (3). In this study we sought to explore which laboratory and cardiac-MRI derived measures are associated with valvular disorders as determined by echocardiography.

Methods: Participants enrolled in the Courtois Cardiovascular Signature Program underwent a CMR scan (3T Premier™, GE Healthcare) and blood testing at baseline. 383 patients with clinically diagnosed Aortic, Mitral, Tricuspid or Pulmonary valve disorders according to American Society of Echocardiography (ASE) standards or in medical records when available were compared to 677 healthy participants. The healthy controls did not have valvular disease according to ASE or medical records. Differences in blood and MRI biomarkers between healthy and diseased participants were tested via one-way ANOVA in RStudio (Vienna, Austria). A one-way ANOVA was conducted to test the difference in means between blood markers across disease outcomes. The detectable effect size was verified by calculating Cohen's d. A power analysis was conducted to determine the sample size and assess the power level of the study. A p-value of less than 0.05 was considered statistically significant.

Results: Patients suffering from valvular disease were matched for age and sex to healthy controls and the means of biomarkers were compared. Apo(b) levels were significantly lower in patients with Aortic Stenosis (n=375, d=0.774, p=2.5e-24), Mitral Stenosis (n=18, d=0.689, p=4.6e-2), Tricuspid Regurgitation (n= 346, d=0.746, p=3.27e-21) and Pulmonary Stenosis (n=273, d=0.691, p=6.94e-15) with moderate effect sizes. Patients using lipid-modifying statins were compared. Those with Aortic Stenosis (n=375, d=0.757, p=5.43e-23) and Tricuspid Regurgitation (n=346, d=0.749, p=4.56e-21) had lower APO(b) levels than those without valve disease. CRP levels were higher in patients with Aortic Stenosis (n=375, d=0.197, p=7.3e-3) and Tricuspid Regurgitation (n=346, d=0.155, p=4.30e-2) with small effect sizes. Lp(a) levels were higher in patients with Aortic Stenosis (n=375, d=0.184, p=1.28e-2) with a small effect size. Lp(a) above 500 was associated to Aortic Stenosis (n=375, $\chi^2=8.8751$, df=1, p=0.002891) and Tricuspid Regurgitation (n= 346, $\chi^2=7.5683$, df=1, p=0.005226).

Conclusion: Our findings indicate that CRP, Lp(a) and Apo(b) have an association to HVD and could have prognostic value. The APO(b) trend could be due to confounding or selection bias, as it does not align with the literature. Further study is needed examining biomarkers and echocardiogram data to better diagnose valve disease.

Source of Funding: The Courtois Cardiovascular Signature Program is supported by the Courtois Foundation and the MUHC Foundation.

36 – Methylation profiling supports diagnosis in undifferentiated uterine malignancies for a more tailored clinical management

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Background: Uterine malignancies show a wide range of different morphologies, molecular profiles, and clinical outcomes. The majority of uterine cancers show good prognosis; however, a subset of these tumors rapidly progress, metastasize, and necessitate aggressive surgical and adjuvant management. Some tumors are associated with familial syndromes and need a specialized genetic workup. Unfortunately, the current diagnostic approach for endometrial malignancy is imperfect and often fails to recognise undifferentiated endometrial carcinoma, a particularly aggressive subtype of cancers. Here we investigate a new diagnostic approach using DNA methylation profiling to see if it could support pathologists to diagnose undifferentiated endometrial malignancies.

Material and Methods: We retrieved a series of high-grade endometrial malignancies with available tumors tissue from a multi-centre cohort. The morphology of each case was reviewed centrally. Immunohistochemical tests were performed to confirm the undifferentiated nature of the tumors. DNA extraction for methylation profiling was performed on all cases. We used the Infinium Methylation EPIC v1.0 and EPIC v2.0 Beadchip assay (Illumina). Unsupervised clustering and t-SNE algorithms were performed to highlight the different methylation profile among our cohort.

Results: We included 81 cases of endometrial cancer, median age 58-year-old. Analysis of the methylation profiling in our series identified three distinct clusters linked to three established diagnoses: endometrial carcinoma (EC), dedifferentiated carcinoma (DDC), and SMARCA4 deficient uterine sarcoma (SDUS). The median age for these subgroups was 55, 65, and 27 year old respectively. The different clusters were also associated with different clinical outcomes. The median overall survival (OS) and progression free survival (PFS) was X, Y, Z years respectively.

Conclusions: Our result support that methylation profiling is a robust approach to help with the diagnosis of undifferentiated endometrial malignancies. These tumors have very different clinical presentation and outcome. Moreover, a diagnosis of SDUS should trigger genetic workup to exclude the possibility of familial syndrome. Going forward we will study the specific methylation difference between these tumor types to help understand their underlying pathogenic mechanisms.

Source of funding: This work was supported by the Marathon of Hope, Clinician Scientist award.

37 - Differentiating Human Bone Marrow Stem Cells Towards Ligamentogenic Lineage Using Physiological Oxygen Tensions and Glucose Concentrations for Tissue Engineering Applications

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Background: Ligament injuries are common musculoskeletal injuries, with approximately 69 injuries per 100,000 persons for the anterior cruciate ligament alone. Due to their hypocellular and hypovascular nature, ligament tissues do not heal and regenerate properly after injury. When conservative management fails, the current gold standard of surgical reconstruction using auto/allografts suffers from high failure, complication, and revision rates. Implantable, stem cell-loaded bioengineered ligament grafts have gained momentum as a potential alternative solution, possibly reducing donor morbidity and increasing long-term success. Human bone marrow stem cells (hBM-MSCs) constitute a popular cell source. Still, spontaneous nonspecific differentiation *in-vivo* into unwanted lineages plays a key role in scaffold non-integration and eventual failure. In addition, ligament tissue and the articular joint space have lower oxygen tensions than arterial and venous levels, and it is critical for optimal tissue physiology and bioengineered graft integration as the grafts grown in standard non-physiological tissue conditions face “adverse conditions” upon implantation. In this study, we hypothesized that culturing hBM-MSCs under optimized near physiological oxygen tensions would enhance their differentiation into the ligamentogenic lineage for use in ligament tissue engineering to improve interventional outcome.

Methods: hBM-MSCs (RoosterBio) were cultured for 10 days at 37°C in Dulbecco’s Modified Eagle Medium (DMEM) supplemented with 5ng/mL TGF- β , 1ng/mL bFGF, and 50 μ g/ml L-ascorbate under atmospheric and standard cell culture (20% O₂), intravenous (5% O₂), and intraarticular (2% O₂) oxygen tensions at 4 different glucose concentrations: 4.50 g/L, 2.25 g/L, 1.00 g/L and 0.50 g/L . Cell-seeded culture plates were placed in a standard incubator with 5% CO₂ at 37°C for atmospheric oxygen tension. For intravenous and intraarticular oxygen tensions, hypoxia incubator chambers (StemCell Technologies) were sealed and flushed with 5% O₂ and 2% O₂ gas premixes, respectively, and placed inside an incubator at 37°C. After 24 hours, mitochondrial staining (M7512, Invitrogen) was done to visualize effects of hypoxia on mitochondrial dynamics and imaged using confocal microscopy (Olympus). Media changes were performed every 3 days, after which the chambers were resealed and reflushed. After 10 days, AlamarBlue™ assay was performed to evaluate the metabolic activity.

Results: Our data shows that metabolic activity of hBM-MSCs significantly decreases with decreasing oxygen tensions for all glucose concentrations using AlamarBlue™ assay readings. Glucose uptake by hBM-MSCs significantly increases with increased oxygen tensions for all glucose concentrations. 3D mitochondrial image analysis shows that hBM-MSCs mitochondria network are fragmented in response to hypoxic conditions.

Significance: These findings suggest that using near-physiological concentrations of glucose and oxygen tensions during differentiation is leading to the metabolic shift of hBM-MSCs towards the native ligamentogenic phenotype. Optimizing culture conditions for differentiating hBM-MSCs into the ligamentogenic lineage would allow us to use these cells in bioengineered ligament grafts for ligament reconstruction. Moreover, maturing these cell-seeded bioengineered grafts under near-physiological conditions potentially enhances their integration at the intraarticular graft site, thus lowering revision rates and enhancing the patient’s quality of life.

38 - Sex specific effects of USP19 KO on disease progression in a mouse model of Alzheimer's disease

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Alzheimer's disease (AD) is the most common neurodegenerative disease, although current therapies remain inadequate. USP19 is a deubiquitinase that affects proteostasis of tau and alpha-synuclein (a-syn), proteins that form aggregates in neurological disorders such as AD and Parkinson's disease (PD). Our lab previously reported that USP19 knockout (KO) in a mouse model of PD decreased accumulation of phospho-synuclein positive aggregates in the brain. In addition, our recent studies on USP19 in a mouse model of AD that expresses a mutant tau that causes disease in humans, demonstrated that loss of USP19 significantly prolonged survival and decreased neurodegeneration and activation of microglia and astrocytes. Since these results were obtained in female mice, my objective was to determine whether these effects are sex specific. Sex specific differences in Alzheimer's disease are well recognized, with AD being more common in women but more severe in men. In contrast to female mice, male USP19 KO had similar survival and brain atrophy as WT mice. Brain sections were stained with antibodies to phospho-Tau (pTau) to detect aggregates, and to the neuroinflammatory markers Iba1 and GFAP to detect microglial and astrocyte activation respectively. Loss of USP19 did not affect any of these parameters in WT compared to KO. As estrogens have previously been observed to induce USP19 expression through an estrogen receptor (ER) α response element in the USP19 gene, the sex specific differences in effects of USP19 in AD may be due to higher levels of USP19 in females. Our results demonstrate the importance of conducting preclinical studies in both sexes and suggest that inhibition of USP19 as potential therapy for AD may be sex specific.

39 - Exploring the pathophysiology of POLR3-related leukodystrophy by generating a disease model using patient-derived iPSCs

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Background: Leukodystrophies (LDs) are a group of rare neurodegenerative disorders characterized by abnormal cerebral white matter. Disease onset is typically in early childhood, leading to progressive loss of function and, ultimately, life-threatening complications. RNA polymerase III-related leukodystrophy (POLR3-HLD) is one of the most common hypomyelinating leukodystrophies (HLDs), characterized by a lack of myelin deposition during development. It is caused by biallelic pathogenic variants in genes encoding RNA polymerase III (Pol III) subunits, including *POLR3A*, *POLR3B*, *POLR1C*, *POLR3D*, and *POLR3K*. Pol III is responsible for transcribing many short non-coding RNAs (ncRNAs), including but not limited to 5S RNAs, tRNAs, and U6 RNA. *POLR1C* is a common subunit of both Pol I and Pol III. In POLR3-HLD, the two studied *POLR1C* mutations have been shown to specifically impair the assembly and nuclear import of Pol III, but not Pol I, leading to decreased occupancy of Pol III at the chromatin. Although Pol I is thought to have a minor contribution to POLR3-HLD disease pathogenesis, previous research has demonstrated that patients with *POLR1C* variants have a higher probability of having craniofacial abnormalities, which is reminiscent of a Pol I disorder, Treacher Collins syndrome (TCS). Recently, *Polr3a* and *Polr3b* mouse models, as well as *in vitro* experiments where *Polr3a*, *3b* & *1c* genes were knock-downed in mouse oligodendrocyte (OL) progenitor cells, have identified defects in the OL lineage, providing the first evidence of Pol III dysfunction resulting in abnormal OL maturation and myelination ability. However, it is still unknown how this lineage is specifically affected and how pathogenic variants in *POLR1C* lead to the HLD phenotype. Here, we hypothesize that *POLR1C* mutations will cause defects in OLs, leading to compromised lineage development and improper myelination.

Methods: To address this, we generated induced pluripotent stem cells (iPSCs) from three patients with bi-allelic pathogenic variants in *POLR1C*. We aim to generate isogenic controls for these patient lines by genetically correcting the pathogenic variants using CRISPR-Cas9. Patient-derived iPSCs and their genetically corrected counterparts will then be differentiated into OPCs and OLs through the delivery of specific growth factors and mitogens. Throughout the differentiation process, immunocytochemistry and qPCR will be used to assess the expression of lineage markers, allowing us to investigate the impact of *POLR1C* mutations on the function of these myelin-producing cells.

Results: Guide RNAs have been designed for the generation of isogenic controls. Preliminary OL investigations in one patient iPSC line have revealed compromised OL lineage development. *POLR1C* patient OLs displayed reduced morphological complexity and a decreased capacity for the ensheathment of neuron-mimicking nanofibers. qPCR results of lineage development have validated the levels of important OL and myelin genes in one patient iPSC line and control.

Conclusion: Our preliminary investigations provide the first insights into the pathophysiology of POLR3-HLD due to pathogenic variants in *POLR1C*. Our future directions involve the development of specific isogenic controls as well as the differentiation of additional patient-derived iPSC lines to fully delineate the breadth of OL defects within this rare disease.

40 - Medical student career choice: a qualitative study of medical students with an interest in obstetrics and gynecology across Canada

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Introduction: Medical students' career choice is influenced by various factors throughout their education. Although studies have explored factors influencing medical students' career choice, few focus on components within an OBGYN curriculum to ensure students have sufficient information about the specialty to make an informed career choice.

Methods: This qualitative study interviewed medical students who expressed an interest in OBGYN to determine factors that led them to such decisions and explore any potential gaps in the existing curriculum. We conducted semi-structured qualitative with medical students of all training levels from all seventeen medical schools across Canada.

Results: Thus far, 8 interviews were conducted (Age = 20-27, Level of training = Pre-medicine to 3rd year medical school, Gender = 87.5% Females & 12.5% Males). Students who chose OB/GYN were significantly influenced by early clinical exposure, mentorship, and perceived work-life balance. Lifestyle considerations, including the ability to balance personal and professional life, were frequently mentioned as a major factor in the decision-making process. Moreover, many participants highlighted the lack of structured OBGYN exposure in their curriculum as a barrier to making an informed career choice. Students stressed the value of hands-on experiences and shadowing, noting early positive interactions with OBGYN professionals solidified their career choice.

Conclusions: This research underscores the importance of incorporating more comprehensive and earlier exposure to OB/GYN in medical school curricula. Enhancing such exposure can assist students in making informed career decisions and ensure a well-distributed physician workforce across specialties. Ongoing interviews will explore the nuance of "work-life balance" further.

41 - Re-wiring a hard-wired sensory neuron's synaptic connectivity

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Precise synaptic connections in neural circuits are essential for optimal performance in the nervous system. Specific molecular cues are required for the establishment of hard-wired circuits, but the molecules involved in precisely defining the synaptic connectivity of an individual neuron is poorly understood. Our lab has identified fewer than 100 cell surface molecules (CSM) can differentiate a mechanosensory neuron from a chemosensory neuron's wiring pattern in *Drosophila melanogaster*. Here, we use a novel technique that utilizes mutually exclusive alternative splicing to conditionally express multiple transgenes in a specific chemosensory neuron, the Gr59d. We find that the Gr59d chemosensory neuron can be re-wired to morphologically resemble the wiring pattern of a mechanosensory neuron through expression of three CSM transgenes, and that expression of more than five CSM transgenes were even more effective. Our results demonstrate that the mis-expression of the differentially expressed genes from one neuron to another is sufficient to re-arrange its axonal targeting pattern.

42 - The role of income and education in the association between Hypertensive Disorders of Pregnancy and White matter hyperintensities

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Background: Hypertension Disorders of Pregnancy (HDP) have been associated with long term brain structure changes. This could be attributed to small vessel disease (SVD) pathophysiology. Socioeconomic factors such as low education and low income have been associated with a higher incidence of HDP. However, whether these factors influence the association between HDP and brain structure changes, particularly in the volume of white matter hyperintensities (WMH) remains unknown. This study aims to determine whether income and education modify the relationship between HDP and WMH volume.

Methods: Among the United Kingdom (UK) Biobank participants, we included 1,484 females aged 40-69 years at the time of recruitment (2006-2010). The included participants had at least one live birth. We compared females with HDP to females with normotensive pregnancies matched on their date of delivery (1:3 case/control ratio). HDP diagnosis was based on the ICD codes and self-reports while WMH, a key marker of cerebral SVD, were based on brain Magnetic Resonance Imaging (MRI) measurements standardized by head size. We applied the generalized linear regression to evaluate the association between HDP and WMH. The role of education and income was evaluated using interaction terms (education*HDP or income*HDP) and stratified analysis by each income and education category. The regression models were adjusted for the following covariates: age at recruitment, number of births, HbA1c (glycated hemoglobin), waist-to-hip ratio, gestational diabetes, depression, and lifestyle factors such as smoking, sleep duration and alcohol consumption.

Results: The sample comprised 371 females with HDP and 1,113 females without HDP aged 50.4 ± 7.3 years and 49.5 ± 7.3 years, respectively at the recruitment. There was no significant difference in the average volume of WMH between the two groups (HDP = 3.5 ± 4.3 Non-HDP = 3.4 ± 5.8 , $P=0.649$). Regarding education, 51.2% of the females in the HDP group and 45.1% in the non-HDP group had lower educational levels (less than *University/College degree*) ($P= 0.03$). For income, 22.9% of the females in the HDP group and 20.6% of females in the non-HDP group had a low annual household income ($< £18,000$) ($P= 0.124$). In the multivariate analysis, no association was found between HDP and WMH and there was no interaction of HDP with education and income. Stratified analysis revealed that among females with *No formal education*, females with HDP developed more WMH than those without HDP ($= 0.7$, 95% confidence interval (CI)=0.2549-1.2062, $P= 0.0026$). In contrast, in females with *O/GCSEs*, *CSEs* (high school) levels of education, those with HDP developed less WMH than females without HDP ($= -0.3$, CI=-0.6420- -0.0259, $P= 0.0336$). In the stratified analysis by income, the association between HDP and WMH was not significant at any level.

Conclusions: The study found no significant overall difference in WMH volumes between female participants with and without HDP, and no effect modification by education or income on this relationship. However, stratified analysis suggested that educational background, but not income, may influence the HDP-WMH relationship, warranting further investigation.

Source of funding: This research is funded by the Heart and Stroke Foundation.

43 - Understanding the role of Orexin receptor 2-expressing cells in energy balance.

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Introduction: The defining hallmark of obesity is the increased levels of adiposity associated with increased hunger and a decreased energy expenditure. The hypothalamus plays a crucial role in regulating appetite and energy expenditure, and amongst the various cell types involved in maintaining energy balance, Orexin (OX)-expressing cells stand out as critically important. OX signalling is a critical regulator of energy homeostasis as the inhibition/removal of the OX neurons produces obesity. Additionally, the use of a OXR2 (Orexin Receptor 2) specific agonist protects mice from developing obesity due to an increase energy expenditure and reduced food intake. While these findings highlight the importance of defining the OX -> OXR2 pathway due to its therapeutic implications, we currently do not have a full characterization of where OXR2 is expressed across the hypothalamus. We hypothesize OXR2 neurons are expressed in multiple hypothalamic sites that regulate appetite and energy expenditure.

Material and Methods: To investigate the expression of OXR2 cells within the hypothalamus, sectioning and immunostaining techniques will be utilised on OXR2 mutant mice, which express green fluorescent protein (GFP) wherever OXR2 is expressed. We will section the mouse brain and quantify expression of GFP-labelled cells across the mouse hypothalamus through florescent microscopy.

Results: We expect OXR2 cells be present in multiple hypothalamic regions that regulate energy balance including the arcuate nucleus, paraventricular hypothalamus and dorsomedial hypothalamus. Additionally, we expect this experiment will show OXR2 neurons are activated by refeeding, particularly OXR2 neurons in the arcuate nucleus and dorsomedial hypothalamus.

Conclusions: The impact of the results will determine the localization of OXR2 neurons within the hypothalamus, which will allow the understanding of the implications of OXR2 neurons in metabolic disorders such as obesity & determine pathways in these cells that can be leveraged to reverse obesity.

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44 - The Transdifferentiating Potential of Myoblasts: Insights into the Cellular Mechanisms of Neurogenic Heterotopic Ossification

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Introduction: Neurogenic heterotopic ossification (NHO) is an abnormal formation of bone in the soft tissues following nervous system injuries. NHO occurs in 10-50% of patients with spinal cord injury (SCI). While the precise mechanism of NHO remains to be elucidated, evidence shows that muscle-derived stem cells of mesenchymal origin, known as fibro-adipogenic progenitors (FAPs), can differentiate into osteoblasts and chondrocytes, leading to heterotopic ossification. However, it is unclear if myoblasts, the precursors of mature muscle cells, can undergo this transformation. We hypothesize that myoblasts can undergo differentiation into osteoblasts, adipocytes, and chondrocytes when cultured in differentiation media in-vitro.

Material and Methods: Primary myoblasts were isolated from quadriceps muscles of 8-10-week-old female C57BL/6J mice using magnetic-activated cell sorting method (MACS). Negative cell sorting was performed with a satellite isolation antibody cocktail, followed by positive cell sorting using alpha-7 integrin antibodies. Myoblasts were then allowed to grow for 14 days, reaching 80-90% confluency. The myoblast culture was then either kept in regular myoblast growth media, or replaced with either osteogenic, adipogenic, or chondrogenic media. The multipotency of myoblasts was then assessed at day 14 and day 21 post trilineage media change. Osteogenic lineage differentiation and mineralization was evaluated using Alizarin Red staining to detect calcium deposits as markers of osteogenesis. Adipogenic differentiation was assessed with Oil Red O staining, which detects lipid droplets. Chondrogenic differentiation was evaluated using Safranin O staining, detecting glycosaminoglycans and proteoglycans in chondrocytes. Quantitative and qualitative image analyses were conducted on the Image J software.

Results: Isolated myoblasts formed myotube after 18 days of culture in regular myoblast growth media. When cultured in differentiation media, myoblasts did not exhibit significant chondrogenic, osteogenic nor adipogenic differentiation at 14 days post trilineage media change. The trilineage differentiation will be further analyzed at 21 days.

Conclusion: Myoblasts are not capable of differentiating into osteoblasts, adipocytes, and chondrocytes after 14 days of culture in trilineage differentiation media. We predict that myoblasts will exhibit signs of transdifferentiation at 21 days. These results provide insights into the multipotency of myoblasts and their potential role in ectopic bone formation.

Source of Funding: Faculty Medicine and Health Science, McGill University; Department of Medicine, MUHC; North American Spine Society; AO Spine North America

45 - Racial disparities in stressful life events among women

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Methods: We analyzed the US Go data, which includes four harmonized cohorts from the United States: (1) Multi-Ethnic Study of Atherosclerosis, (2) Cardiovascular Health Study, (3) Women's Health Initiative, and (4) Framingham Heart Study. We included only female participants enrolled in these studies between 1948 to 2002. SLE was derived from responses in the individual study questionnaires that asked about the occurrence of traumatic events in the past year such as death of a loved one, divorce, financial issues, adverse medical conditions among others. Participants were stratified by age group (41-50, 51-60, 61-70, 71-80, >80 years), race (White, Black, Other), and SLE level (low, moderate, high). A heatmap was developed to visualize the proportions of SLEs reported across subgroups, and a descriptive table was created to summarize the findings.

Results: Black participants reported the highest proportions of high SLEs across almost all age groups, compared with White participants, especially those aged 51-60 (23% vs 15%) and 61-70 (22% vs 19%). Approximately 21% and 19% of the "other" racial group participants aged 51-60 and 61-70 reported high SLEs, respectively. While the percentage of participants who reported low SLEs was less than 11% across racial groups, White participants generally reported higher levels of low SLEs compared to Black and Other racial groups.

Conclusions: The findings suggest that middle-aged Black are more likely to experience high levels of SLEs than White or Other racial groups. This difference in high experience SLE may contribute to the observed racial disparities in the incidence of CVD.

46 - Understanding The Molecular and Neural Function of Transcription Factor 20 (Tcf20)

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Background: Autism spectrum disorders (ASDs) are a group of neurodevelopmental disorders (NDDs) affecting 1 in 66 children in Quebec. A novel cause of ASD is TCF20-associated neurodevelopmental disorder (*TAND*), resulting from mutations in the *Transcription Factor 20 (TCF20)* gene. *TAND* is characterized by hypotonia, intellectual disabilities, seizures, and ASD features. Preliminary studies using a mouse model with germline haploinsufficiency of *Tcf20* have shown that these mice exhibit *TAND*-like features, including ASD-like behaviors, abnormal brain weight, and neuron differentiation and proliferation issues. Due to *Tcf20*'s broad expression and varied roles across different cellular contexts, there is a pressing need to understand the molecular and neural mechanisms underlying these conditions. We have acquired *Tcf20^{Flox}* mice to manipulate *Tcf20* expression across different neuron cell types by crossing them with various Cre mouse lines. Our aim is to dissect *Tcf20*'s roles in diverse neural cell types, enhance our understanding of its contribution to *TAND*, and potentially guide development of targeted therapeutic strategies for neurodevelopmental disorders in the future.

Materials and Methods: To determine the impact of brain cell-specific *Tcf20* knockout, we crossed the *Tcf20^{Flox}* mice with various transgenic Cre lines such as *Emx1^{Cre}* for cortical excitatory neurons, *Vglut2^{Cre}* for subcortical excitatory neurons, and *VGAT^{Cre}* for inhibitory neurons. These crosses aim to generate control lines (Cre+ only) and both heterogeneous (HETE) and homogeneous (HOMO) *Tcf20* knockout lines in these distinct neuronal populations, with *Tcf20* presence confirmed by genotyping. The region-specific knockout of *Tcf20*, including the motor cortex, hippocampus, thalamus, and striatum, was confirmed using immunostaining and quantitative PCR (qPCR). We evaluated general health changes post-knockout, such as body weight, survival rate, and metabolism in both sexes. Behavioral changes related to *TAND* were studied in five aspects: motor ability, memory function, anxiety, ASD-related behaviors, and epilepsy.

Results: Immunostaining and qPCR data confirmed a flox-dependent decrease in *Tcf20* distribution across control, heterozygous deletion, and homozygous deletion groups. Preliminary findings from *Emx1^{Cre}; Tcf20^{Flox}* male mice displayed *TAND*-related phenotypic changes, including decreased body weight, reduced marble burying, and increased social dominance after *Tcf20* knockout. Conversely, *Vglut2^{Cre}; Tcf20^{Flox}* male mice demonstrated decreased body weight with a 70% survival rate. Behavioral assessments of *Vglut2^{Cre}; Tcf20^{Flox}* revealed reduced latency to fall in the Rotarod test and decreased marble burying across both sexes. Interestingly, *Vglut2^{Cre}; Tcf20^{Flox}* mice showed reduced performance in the pole test, a result not observed in the *Emx1^{Cre}; Tcf20^{Flox}* group. Further behavioral studies are ongoing to deepen our understanding of *Tcf20*'s influence across these models.

Conclusions: Our findings highlight the significant impact of *Tcf20* knockout in cortical and subcortical regions. Differences between the *Emx1^{Cre}; Tcf20^{Flox}* and *Vglut2^{Cre}; Tcf20^{Flox}* groups reveal *Tcf20*'s varied roles in different glutamatergic neurons. This underscores the potential of targeting specific brain regions to regulate associated neurodevelopmental disorders. Confirming *Tcf20* knockout in various brain regions correlates *Tcf20* with neurodevelopmental phenotypes, guiding the development of brain region-targeted therapeutic strategies for *TAND* and ASD-associated neurodevelopmental disorders.

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47 – Impact of Social Determinants of Health on Arterial Stiffness in High-risk Preeclampsia Pregnancies

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Background: Preeclampsia is a serious disorder of pregnancy characterized by hypertension and organ damage affecting up to 8% of pregnancies. Since 1989, the incidence of preeclampsia doubled in Quebec following the increasing trends of obesity, diabetes, and advanced maternal age. Results of our REVEAL study showed that a strong indicator of preeclampsia risk is arterial stiffness (AS), a property of arterial walls that indicates arterial elasticity. Carotid-femoral pulse wave velocity (cfPWV) is the gold standard measure of AS, with a 1m/s increase observed within the first trimester being associated with a 64% increase in odds for preeclampsia. AS is influenced by many factors, such as age and body mass index, but social determinant of health (SDoH) of race, socioeconomic status and baseline anxiety or depression have been shown to also have an effect. Recently, race and socioeconomic status have also been implicated as risk factors for preeclampsia. Other SDoH related to social and economic stability, such as marital status, relationship length, immigrant status, employment status and education level have been implicated as potential contributors to preeclampsia. However, their potential impact on AS not been examined in pregnancy. Thus, this study aims to characterize the relationship between these SDoH and AS in pregnancies at high-risk for preeclampsia.

Methods: Participants were recruited through our multinational PULSE Study (MP-37-2021-6854) following informed consent guidelines in 9 obstetric clinics across Canada, the UK and USA. Eligible individuals had singleton pregnancies, <14 weeks gestation, and at least 2 moderate-risk factors or 1 high-risk factor according to the U.S. Preventative Services Task Force guidelines. Exclusion criteria included multiple pregnancy, >14 weeks gestational age, and a history of stroke, heart disease or peripheral arterial disease. Individuals were evaluated at 10-13⁶ weeks and 18-21⁶ weeks, where AS assessment was performed through applanation tonometry, and psychosocial information was collected via validated questionnaires. Mean cfPWV (m/s) was collected at each visit. Questionnaire data were then examined, identifying participant marital status, relationship length, immigrant status, employment status and education level as SDoH variables of interest. The development of preeclampsia was analyzed as an outcome of interest. Linear regression analysis was performed to evaluate the association between SDoH and cfPWV, and logistic regression was used to identify the odds for preeclampsia development based on SDoH variables. All statistical analyses were performed using SPSS, edition 29 (IBM, Armonk, New York, USA) software.

Conclusion/relevance: This study provides valuable insight into how SDoH factors, can alter AS and contribute to preeclampsia. Future research will extend this project to account for limitations in the preliminary analysis and adjust for relevant cofounders (age, BMI, etc.). Furthermore, it may allow for research into mechanisms and ultimately targeted strategies to prevent preeclampsia. This could then be implemented into clinical assessments to improve pregnancy outcomes and comprehensive care.

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48 – Development and in vitro validation of an automated image-based batch analysis methodology; leveraging patient-derived organoid-based assays for precision oncology.

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Introduction: Esophageal adenocarcinoma, originating at the esophagogastric junction (EGJ), is highly aggressive with a five-year survival rate below 20%, underscoring the urgent need for better therapies. Currently, the only standard of care for locally advanced disease comprises systemic cytotoxic peri-operative docetaxel-based triplet chemotherapy before and after surgical resection. The effectiveness of this treatment is assessed through imaging techniques (e.g., PET scans) to observe changes in tumor size (objective response) and through microscopic examination of resected tumor tissues for viable tumor cells (pathological response), though these methods often provide inconsistent results. To improve response predictions and screen for new therapies, patient-derived tumor organoids (PDOs) grown in a three-dimensional matrix are utilized. *In vitro*, these organoids serve as miniatures of the originating tumors, providing a robust platform for studying both pathological responses, validated through assays like Cell-Titer Glo™, and objective responses, tracked by morphological changes in PDOs pre- and post-drug exposure using brightfield microscopy.

Methods: This project involved the creation of an objective, automated batch analysis methodology with custom macros in ImageJ to track and quantify morphological changes in patient-derived tumor organoids (PDOs) throughout the treatment process. This advanced approach significantly improves the precision and consistency of measurements over traditional, manual assessment methods, which are often laborious and error prone. The software was validated using a comprehensive training set of existing PDO images, ensuring the software's capability to accurately locate organoids and measure various parameters such as size and roundness. Here, we report on the application of this methodology to 2 experimental scenarios:

1. PDOs were treated to a clinically-equivalent single cycle of cytotoxic FLOT chemotherapy for 24 *in vitro* and their morphology and count were monitored before and after exposure;
2. The effects of conditioned media enriched with lipids, proteins, and metabolites from cancer-associated fibroblasts (CAFs), from poor- vs. good-responder patients on PDOs were investigated, and compared to non-conditioned medium as a control, with the goal of understanding tumor-supporting or -inhibiting roles of CAF-secreted factors.

Results: The automated system processed over 500 images per hour, enabling precise measurements of morphological changes in PDOs from various treatments. After exposure to a cycle of FLOT chemotherapy, PDOs typically exhibited a reduction in size, aligning with expectations of treatment efficacy. These changes were documented and correlated with in-patient objective responses to validate the model's predictive accuracy. The study also explored the impact of conditioned media from cancer-associated fibroblasts (CAFs). Organoids exposed to media from CAFs showed an increase in size, suggesting a tumor-supportive role of the secreted factors. This contrasted with the shrinkage from FLOT treatment and provided insights into the dual influences of chemotherapy and microenvironment factors on tumor organoid behavior, which offers potential pathways for therapeutic interventions based on microenvironment modulation.

Conclusion: The integration of PDOs with image analysis has robustly correlated *in vitro* organoid responses with clinical outcomes. This correlation enhances the predictive power of the organoid model, offering significant improvements in the accuracy of treatment response predictions and the potential to tailor therapeutic strategies more effectively to individual patient needs.

49 – The QLC+ study: A Journey to Diagnosing COPD

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Background: COPD is one of the top 3 causes of death worldwide, yet it is currently underdiagnosed. It is a pulmonary disease that causes shortness of breath, coughing, chest tightness, the production of mucus and ultimately results in airflow limitation. Untreated COPD is associated with increased hospitalization and deterioration of the disease which increases visits to the emergency department and causes a high burden on the healthcare system. There is only one available test to diagnose COPD currently and it comes with long waiting lists. Smokers are the most at risk for this disease as smoking is the bigger risk factor, however, lots of smokers underreport their symptoms making it even harder to diagnose them. Therefore, to increase the rates of diagnosis of COPD and most importantly the early detection of the disease, one has to do 2 things; identify the population most at risk and find a faster method of diagnosis.

Methods: An alternative method to diagnose COPD is to look for markers of COPD on a CT scan such as emphysema i.e. small holes in the lungs and thickening of the airways and to ask the patients COPD-specific questions on their health to determine if they are symptomatic or not. As for the population, the Quebec lung cancer screening program invites all smokers between the ages of 55 to 74 years old, who are at risk of lung cancer according to clinical scores, to get a low-dose CT scan to determine if they indeed have cancer. This population constitutes a perfect target for COPD as they have the main risk factor contributing to the disease. Therefore, patients are enrolled in our study to determine if using this alternative method along with informing their family doctors of our findings would potentially increase the rate of diagnosis and get the patients started on a treatment for COPD to alleviate their symptoms and improve their quality of life.

Conclusion: COPD treatment aims to improve patient symptoms, decrease exacerbations, decrease mortality and improve daily functioning and quality of life. CT scan findings of COPD are reported, however unprompted, healthcare providers rarely act on this information due to the high burden and increasing demands on providers. Therefore, we aim to test a personalized health intervention nested within the Quebec lung cancer screening program, which will diagnose COPD, educate the patients about the disease and its implications as well as recommend pharmacological treatment for symptomatic patients to their healthcare providers.

Future: Including a diagnosis of COPD in the lung cancer screening program process, using the CT scans that are already performed for lung cancer, would be a big step forward in faster diagnosis and treatment. It will save the time lost waiting on a spirometry test and allow an earlier detection of the disease.

1 - NMDA receptors determine spine density of cortical layer-5 pyramidal cells

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Introduction: N-methyl-D-aspartate receptors (NMDARs) are glutamate receptors that play a major role in synaptic transmission and plasticity. For instance, NMDARs are understood as coincidence detectors of simultaneous pre- and postsynaptic activity, making them a key player in Hebbian plasticity, a process which underlies learning and memory. Additionally, NMDAR dysfunction is linked to neurological and psychiatric disorders such as Alzheimer's disease and schizophrenia, making them a promising target for drug therapy. However, the precise contribution of these receptors on synapse formation remains unclear. Here, I investigated the impact of sparse early postnatal NMDAR deletion on dendritic spine density in mouse layer 5 (L5) pyramidal cells (PCs) of the primary visual cortex. I hypothesized that genetic NMDAR deletion would reduce spine density in L5 PC basal dendrites.

Material and Methods: To sparsely delete NMDARs in L5 neurons, the visual cortex of postnatal day 0-1 NR1^{fl/fl} mice was injected with AAV-eSYN-mCherry-T2A-iCre-WPRE virus. I stained biocytin-loaded patch-clamped cells with fluorescent dye-conjugated streptavidin and acquired 3D confocal image stacks of PCs, based on which I manually counted basal dendritic spines. Statistics was carried out in Igor Pro.

Results: Basal dendritic spine density was indistinguishable in wild-type (WTs: 2.4 ± 0.1 spines/10 μm , $n = 40$) and knockout cells (KO: 2.1 ± 0.1 spines/10 μm , $n = 37$, $p = 0.08$). This seemed inconsistent with prior work in the lab, showing that global KO in all PCs using Emx1^{Cre/+};Grin1^{fl/fl};Ai9^{fl/+} mice reduced spine density (WT: 3.8 ± 0.2 spines/10 μm ; KO: 3.0 ± 0.2 spines/10 μm , $p < 0.01$). Sparse KO, however, did reduce spine density in tertiary branches (WT: 2.5 ± 0.3 spines/10 μm , $n = 7$; KO: 2.1 ± 0.2 spines/10 μm , $n = 3$, $p < 0.005$), like in global KO (WT: 3.8 ± 0.2 spines/10 μm , $n = 40$; KO: 3.0 ± 0.2 spines/10 μm , $n = 41$, $p < 0.01$).

Conclusions: The apparent discrepancy between sparse and global deletion may arise because my preliminary data set is too small to detect a difference. However, sparse and global KO outcomes agreed that NMDAR KO reduced spine density specifically in tertiary branches. Furthermore, with sparse KO, both WT and KO cells are in NMDAR-deletion environment, which might impact spine formation in WT cells as well. In agreement, PC basal dendritic spine density in both WT and KO cell was lower in sparse KO than in global KO mice (data not shown). To test the idea that sparse KO affects PCs with intact NMDARs, I will next investigate if spine density correlates with KO sparsity, which varies appreciably across sparse-deletion mice. I will also measure spine density in no-injection control NR1^{fl/fl} mice. Overall, my findings suggest that NMDARs determine spine density of cortical layer-5 pyramidal cells. My project will thus provide insight into how NMDARs contribute to structural development and connectivity in neocortical circuits.

2 - The Role of Endoplasmic Reticulum Stress in ET-1 Induced Vascular Dysfunction in Hypertension

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Background: Hypertension is a multifactorial and complex disease characterized by blood pressure $\geq 140/90$ mmHg and is a leading cause of morbidity and mortality worldwide. It is associated with vascular dysfunction, characterized by endothelial dysfunction, vascular hypercontractility, vascular hypertrophy, fibrosis, inflammation, and calcification. Vascular smooth muscle cells (VSMCs), the predominant constituents of the arterial vessel wall, are key players in vascular dysfunction associated with hypertension. Vasoactive peptides play an important role in vascular dysfunction in hypertension. For example endothelin-1 (ET-1), a potent vasoconstrictor involved in vascular remodeling through increasing contraction and proliferation of VSMCs. It has been demonstrated that ET-1 is associated with endoplasmic reticulum (ER) stress (ERS) in experimental models of chronic kidney disease and pre-eclampsia. ERS occurs when there is an accumulated of misfolded proteins in the ER. This initiates an Unfolded Protein Response (UPR), activating three separate pathways (protein kinase RNA-like ER kinase (PERK), inositol-requiring protein 1 α (IRE1 α) and activating transcription factor 6 (ATF6)) in an attempt to return the ER to its normal physiological state. Chronic ERS triggers the UPR, leading to inflammation, autophagy or apoptosis. It has been previously reported that ERS plays a role in the pathogenesis of hypertension. Studies have shown that inhibiting ERS improves vascular dysfunction in angiotensin II-induced hypertension, reduces systolic blood pressure and normalizes aorta contraction in Stroke-prone Spontaneously Hypertensive Rats (SHRSP) rats. However, the underlying mechanism of ERS remains unclear.

Aim: We hypothesize that in hypertension, ET-1 induces ERS leading to dysregulation of contractile and proliferative signaling pathways in VSMCs contributing to vascular dysfunction. Therefore, we aim to investigate ET-1-induced VSMC signaling in hypertension.

Methods: VSMCs from mesenteric arteries of normotensive Wistar- Kyoto rats (WKY) and SHRSP rats were used. Expression of ERS markers (ATF4, XBP1), activation of pro-contractile signaling molecules (MLC20) and growth (ERK1/2) were assessed by immunoblotting after ET-1(100nM) stimulation in the presence or absence of ERS inhibitors (4-PBA, chemical chaperone, 1mM; STF083010, IRE1 inhibitor, 60uM; GSK2606414, PERK inhibitor, 5uM). Vascular function was measured by wire myography in mesenteric arteries from SHRSP.

Results: Our previous studies investigated the expression of ERS markers in VSMC from WKY and SHRSP. Expression of XBP1, downstream of the IRE- 1 pathway, and ATF4 downstream of the PERK arm of UPR were increased in cells from SHRSP. Next, we investigated whether ET-1 induces ERS in cells from WKY rats. We observed a significant difference between in ATF4 expression in cells treated with ET-1 for 16h and 24h. My studies then assessed the effect of ERS inhibitors (STF, GSK, 4-PBA) on ET-1 signaling. Our results showed that ERS inhibitors decreased ET-1 induced phosphorylation of MLC and ERK in VSMCs from SHRSP. In addition, ET-1 (E_{max} 72.38 $\pm$ 5.29 and 4.18 $\pm$ 0.64 vs DMSO 134.9 $\pm$ 7.07) and U46619 (E_{max} 70.93 $\pm$ 3.96 and 8.89 $\pm$ 1.16 vs DMSO 95.11 $\pm$ 5.58) elicited contraction were inhibited by GSK and STF ($p < 0.001$ vs control) in SHRSP.

Conclusion: In conclusion, we have shown that ET-1- mediated signaling involves ERS, which may contribute to vascular injury in hypertension.

3 - Clinical Isolates of *Pseudomonas aeruginosa* from Cystic Fibrosis Patients are Susceptible to Ofloxacin, Levofloxacin, Ciprofloxacin, and Moxifloxacin

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Introduction: Seventy-nine strains of *Pseudomonas aeruginosa* were isolated from the lungs of 17 cystic fibrosis patients over 20 years. The strains isolated from each patient are clonally related, suggesting decades-long persistence despite treatment with antibiotics. These strains were screened for antibiotic resistance to ofloxacin using a minimum inhibitory concentration (MIC) assay. Antibiotic resistance occurs when bacteria evolve to evade the effect of antibiotics through various mechanisms. However, these strains were inhibited by ofloxacin at concentrations less than or equal to 4 µg/mL, indicating non-resistance. We aim to screen these 79 strains against more clinically-relevant fluoroquinolones, including levofloxacin, ciprofloxacin, and moxifloxacin, to confirm susceptibility. If these strains fail to display resistance, further investigation will be required to explain their continued presence in the lungs. One possibility is that these strains are antibiotic tolerant as opposed to resistant. Antibiotic tolerance often occurs when an essential bacterial process is slowed, allowing bacteria to survive exposure to antibiotics at concentrations that are otherwise lethal.

Methods: Susceptibility of the isolates was confirmed using a minimum inhibitory concentration (MIC) assay. Antibiotic assay plates were prepared with concentrations ranging from 16 µg/mL to 0 µg/mL. Clinical isolates were grown from glycerol stock onto LB agar and incubated overnight (18h) at 37°C. They were then resuspended in CAMHB media, diluted to an OD₆₀₀ of 0.001, and inoculated onto the prepared plate. Final antibiotic concentrations ranged from 8 µg/mL to 0.125 µg/mL. Plates were incubated overnight (18h) at 37°C, then moved to a shaking incubator (37°C) for 15 minutes, before being moved back to the static incubator (37°C) for 2 hours. Finally, plates were visually assessed for turbidity. The lowest concentration of each antibiotic that showed no growth was recorded as the MIC.

Results: Overall, only two of the 79 ofloxacin-susceptible strains displayed resistance to other drugs: DNC1 to ciprofloxacin and DNC62 to moxifloxacin. None of the other strains displayed resistance to any other fluoroquinolone. The strains also appear to have similar resistance levels to levofloxacin and ciprofloxacin (median MIC of 0.5 µg/mL for both), and similar resistance levels to ofloxacin and moxifloxacin (median MIC of 2 µg/mL for both). However, previous testing gave a median levofloxacin MIC of 1 µg/mL, with 43% of MIC values being significantly different from recent values. This indicates a potential error in antibiotic stock preparation and warrants further testing.

Conclusions: This data suggests that susceptibility to the fluoroquinolone ofloxacin can indicate susceptibility to other, more clinically-relevant fluoroquinolones. The 79 strains of *Pseudomonas aeruginosa* broadly display susceptibility to ofloxacin, levofloxacin, ciprofloxacin, and moxifloxacin. Further assays need to be performed to identify strains that display a tolerance phenotype. These assays are often performed at 2-3 times the MIC, so this data will be used in further testing of the clinical isolates.

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4 - Risk Factors for Hospital Admission of Elderly Cancer Patients Presenting in the Emergency Department

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Background: The growing geriatric oncology population presents challenges for emergency departments (EDs). ED overcrowding is associated with an increased risk of adverse events, delays in admission and mortality, particularly for this vulnerable group characterized by frailty and complex care needs. This study aimed to identify key patient characteristics at triage that predict hospital admission among elderly cancer patients in the ED, facilitating early intervention and resource allocation.

Methods: We conducted a retrospective analysis of ED visits from patients who presented to the McGill University Health Center's Royal Victoria Hospital between January 1st, 2014, and December 31st, 2023. Data on initial presentation (e.g. triage vital signs, reason for visit, past medical history, demographics, and others) were extracted. We excluded variables with missing data exceeding 10%. Univariate analysis using Chi-square tests for categorical variables and T-tests for continuous variables (with Bonferroni correction for multiple comparisons) identified factors associated with admission (p-value < 0.05). Statistically significant variables were included in a multivariate logistic regression analysis to identify the most influential factors.

Results: A total of 14,569 ED visits were analyzed, with 6,435 resulting in hospital admission. Of the 62 initial variables, 35 remained after filtering. Univariate analysis identified 26 factors associated with hospital admission. Specifically, triage measurements such as respiratory rate** (mean of 20.43 breaths per minute vs. 18.44 in admitted vs. non-admitted patients, respectively), heart rate** (89.11 bpm vs. 82.26), blood pressures [systolic** (129.57 mmHg vs. 139.60), diastolic** (70.87 mmHg vs. 74.51), mean** (90.11 mmHg vs 95.87)], temperature* (36.89°C vs. 36.77), oxygen saturation** (95.95% vs. 96.71%), glucose level documentation** (35.06 % vs. 25.00%), Glasgow Coma Scale documentation* (28.08% vs. 25.06), supplemental oxygen requirement** (16.29% vs. 3.50%), triage acuity score** (Score of 2.74 vs. 3.02), arrival mode (walking** (42.38% vs. 65.29%), ambulance** (52.35% vs. 31.49%)), prior ED visits (within the past year** (63.82% vs. 55.63%), admission during last visit** (38.98% vs. 22.63%), medical history (infectious** (16.19% vs. 7.33%), respiratory** (24.62% vs. 18.19%), gastrointestinal* (17.72% vs. 15.61%), endocrine* (26.82% vs. 22.42%), hematological* (15.02% vs. 12.19%) diseases), reason for visit (cardiac/respiratory** (24.93% vs. 13.78%)), and cancer type (breast** (16.33% vs. 20.97%), gastrointestinal* (21.69% vs. 18.59%), respiratory** (19.28% vs. 13.03%)) were significantly associated with admission. *p-value < 0.05; ** p-value < 5e-10. Multivariate logistic regression analysis identified five key predictors of admission: supplement oxygen delivery, use of a transport modality to arrive to the ED, past medical history of infectious diseases, prior ED admission, and triage acuity score. The model explained 20% of the variance in admission (R-squared = 0.2).

Conclusions: This study identified key patient characteristics at triage associated with hospital admission among elderly cancer patients in the ED. While these factors contribute to predicting admission, the low R-squared value suggests that incorporating a longitudinal modeling approach with data from the entire course of ED visits, rather than just triage information, may improve predictive accuracy. These findings provide a foundation for developing a machine learning model to assess admission risk, facilitating early intervention and resource allocation.

Source of Funding: McGill student summer bursary and the MUHC Foundation.

5 - Assessing Negative Dominance of Truncated ECI1 Enzyme in Prostate Cancer Cells

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Background: Prostate cancer (PCa) is the second most common cancer in men, affecting approximately 1 in 8 men globally. The survival rate for localized PCa is around 100% but drops to about 28% when the cancer metastasizes. Current clinical indicators like tumor grade, stage, and serum prostate-specific antigen levels do not reliably predict whether a tumor will remain indolent or become metastatic, underscoring the need for better biomarkers. Additionally, there is an urgent need to develop new treatments for metastasized prostate cancer, as existing options are limited and not curative. Genomic alterations, such as gains at the 16p13.3 locus where the ECI1 gene is located, are common in PCa metastases. ECI1 is an enzyme essential for fatty acid beta-oxidation (FAO), a key energy source for PCa tumors. Although the specific role of ECI1 in prostate cancer remains unclear, overexpression of ECI1 has been linked to increased cell growth, motility, tumor size, and metastases, along with higher Gleason grades and lower survival rates, indicating its potential as a biomarker and therapeutic target. Interestingly, a truncated form of ECI1, lacking the first 59 amino acids ($\Delta 59$ ECI1), has been shown to inhibit the replication of viruses relying on FAO, suggesting it may act as a dominant negative form of ECI1. We hypothesize that the truncated ECI1 enzyme acts as a dominant negative in PCa cells and would counter the protumorigenic effects of full length ECI1. The goal of this project is to assess the functional impacts of $\Delta 59$ ECI1 in PCa cells.

Methods: $\Delta 59$ ECI1 cDNA will be PCR-amplified with specific primers for the truncated enzyme, and then cloned into a plasmid expression vector (pcDNA6). Bacteria will be transformed with the plasmid and positive clones will be selected and verified through restriction digestion and agarose gel electrophoresis, followed by large-scale plasmid preparation and sequence verification. PCa cells naturally expressing ECI1 will be transfected with the $\Delta 59$ ECI1 vs control empty plasmid constructs, and expression will be confirmed via immunoblotting. Cell growth will be monitored using a live-cell imaging system, and mitochondrial function (FAO) will be assessed by measuring basal and maximal oxygen consumption rates to assess whether $\Delta 59$ ECI1 is a true dominant negative.

Results: The PCR has been successfully completed, yielding a product of expected size. The cloning of the PCR amplified cDNA into the expression vector is in progress. Once the truncated enzyme's presence is confirmed in the expression vector, we will proceed with the assessment of the $\Delta 59$ ECI1's effect on cell growth and metabolic activity in cancer cells. If our hypothesis is correct, the $\Delta 59$ ECI1 expressing cells should have a reduced cell growth and enzymatic activity compared to the control vector, which would indicate its negative dominance on the endogenous ECI1.

Conclusions: If $\Delta 59$ ECI1 is in fact a dominant negative, it will help us better understand the function of the ECI1 gene in prostate cancer and could eventually serve to develop a targeted treatment for the disease.

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6 - Gender and regional inequities in oral and poster presentations at an international transplant congress

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Background: There are gender and regional disparities in academia as women and authors from low- and middle-income countries are underrepresented in scientific publications. How they intersect is not well characterized given the selective and conventional nature of articles accepted for publication in scientific journals. Examining conference abstract presentations may inform this line of inquiry. Thus, we aimed to characterize gender disparities by country income level in abstract presentations at the 2022 annual congress of The Transplantation Society.

Methods: We included all accepted oral and poster presentations published in the Transplantation journal in 2022. We extracted the first and last names of the first and last authors and their country based on their affiliations. The 2022 World Bank classification was used to characterize country income level. Gender was predicted using Genderize.io and only those where the gender was predicted with >95% probability were included in the analysis.

Results: In 2022, there were 735 oral sessions and 420 posters. For 17 abstracts there was only one named author. Majority (92%) of abstracts originated from high-income or upper-middle income countries (Figure). The gender of 2216 individuals were predicted with >95% probability and were included in the analysis. Overall, 36% women were listed as first or last authors; however, 43% of the first authors were women while only 29% of the last authors were women. Also, while the proportion of women first and last authors was higher among higher-income countries, they lagged behind the proportion of men first and last authors (Table).

Conclusion: There are inequities in knowledge dissemination at the academic congress and gender disparities are noted across all income levels to varying extent. A better understanding of factors contributing to this observation may help advance equity in academic transplantation and progress and strengthen the field of transplantation globally.

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7 - Rapid variant classification in primary ciliary dyskinesia genes by use of zebrafish models

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Introduction: Primary ciliary dyskinesia (PCD) is a mainly autosomal recessive orphan disease (OMIM# 244400) characterized by motile ciliary dysfunction resulting in chronic respiratory tract infections and effects on embryogenesis, including organ laterality defects (e.g. *situs inversus totalis* or *situs ambiguus*). A suspected diagnosis of PCD can be supported by measuring patient's nasal nitric oxide levels or by visualizing ciliary ultrastructural changes on transmission electron microscopy, but the current diagnostic mainstay is via molecular analysis of more than 50 genes that are associated with PCD (Shapiro *Am J Respir Crit Care Med* 2018). However, around 30% of children with clinical features consistent with PCD lack a molecular diagnosis due to frequent variants of uncertain significance (VUS) on genetic testing (Leigh *Transl Sci Rare Dis* 2019). Unfortunately, the absence of an established molecular diagnosis precludes these patients from access to novel personalized treatments and to reproductive risk counseling. Hence, there is a pressing need for the development of functional validation tests for unresolved PCD gene variants. Zebrafish are an ideal model to assess genetic developmental disorders due to their high homology to humans (~70%), their rapid *ex utero* development, and easily visualized internal structures. Additionally, PCD genes such as *dnaaf1*, *dnaaf3*, and *dnah1* have already been studied in zebrafish, with established organ laterality phenotypes.

Aim: The Zebrafish Variant Resolution (ZeVaR) program aims to use zebrafish to rapidly classify VUS by patient-specific mRNA's ability to rescue an observed phenotype. We will knock down *dnaaf1*, establish an associated phenotype, and attempt to rescue by injecting with patient-specific VUS human mRNA.

Methods: Public BLAST databases were used to analyze sequence alignment for functional domain homology. Directional cloning was used to create patient-specific *dnaaf1* variants with zebrafish-optimized pT3TS backbone. Knockdown of *dnaaf1* expression by microinjections of antisense morpholino (MO) oligonucleotides in single-cell embryos, as well as co-injection with wildtype, pathogenic, or VUS *dnaaf1* human mRNA were used to assess the pathogenicity of the VUS. Use of mRNA *in situ* hybridization against *myl7*, a cardiac marker, allowed for visualization of the heart and assessment of organ laterality defects at 48 hours post fertilization (hpf).

Results: BLAST sequence alignment of the VUS functional domain shows 68% similarity between zebrafish and humans, supporting use of the zebrafish model. Preliminary *dnaaf1* knockdown experiments resulted in 35% of the embryos with the *situs inversus* phenotype at 24hpf. Furthermore, *dnaaf1* morphants exhibited a significant increase in perturbed otolith formation and hydrocephalus. Previous experiments suggest rescue of *situs inversus* using a wildtype mRNA co-injection with *dnaaf1* MO, with only a 10% rate of *situs inversus*. Preliminary data shows the *dnaaf1* VUS, Asn225Lys, cannot rescue *situs inversus* in the *dnaaf1* morphants, suggesting the variant's pathogenicity.

Conclusion: There is preliminary evidence to suggest that zebrafish can be used to rapidly classify VUSs in PCD genes by knocking down gene expression using MO, and attempting phenotype rescue with human, patient-specific mRNA.

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8 - MEG Study of Frequency-Tagged Stimuli in Binocular and Pattern Rivalry

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Introduction: Perceptual illusions offer insights into how the visual system operates. During multistable perception, images remain constant while our perception alternates. Binocular rivalry (BR) occurs when two distinct, non-fusible images (such as red and green orthogonal gratings) are presented to each eye. Participants experience phases of almost complete dominance of one image while the competing image is suppressed. Monocular pattern rivalry (PR) occurs when rivaling stimuli (such as transparently superimposed red and green orthogonal gratings) are presented to the same eye. Frequency-tagged visual stimuli are a powerful tool in neuroimaging, enabling the filtering of brain responses at specific fundamental frequencies. For example, each grating in BR and PR flickers at frequencies of 5 or 6.67 Hz, facilitating the analysis of steady-state visual evoked potential (SSVEPs). These eye- or stimulus-specific responses are captured using Magnetoencephalography (MEG).

Methods: The MEG facility at the McConnell Brain Imaging Center (BIC), when combined with anatomical MRI, provides high temporal and spatial resolution. We recorded subject' perceptual reports and brain activity (N=30) while viewing BR or PR stimuli, or control conditions with similar but non-rivalrous stimuli. Psychtoolbox-3 software was used for image presentation, and MEG data was analysed with Brainstorm and MATLAB. Data analysis required pre-processing and artifact removal (for cardiac, eye movements and dental noise). The event related analysis for dominant and suppressed percepts produced time-locked SSVEP responses, with baseline normalized power (z scores).

Results: Behavioral findings show that the mean duration of dominant percepts is ~1.5 sec for PR compared to ~1.8 sec for BR. However, subjects spent more time in transition between percepts (so-called mixed percepts) for PR than for BR (2.5 sec compared to 1.1 sec). MEG-SSVEPs show the strongest magnitude of response to our tagged frequencies in the primary visual cortex and extrastriate regions.

Moreover, the difference between evoked power for dominance vs. suppressed percepts is less for PR than observed for BR. In other words, the depth of rivalry is lower for PR (it is a weaker form of rivalry). As expected, for the non-rivalrous control conditions, the MEG power difference between alternated percepts is less for PR or BR. Our final examination will compare the SSVEP response for stimuli (BR or PR) that have an interocular grating orientation difference of 90 versus 30-degrees. We know that rivalry is behaviorally slower for the 30 deg condition, but it has not yet been demonstrated physiologically that the depth of rivalry is less.

Conclusions: The bistable nature of monocular pattern rivalry is similar to binocular rivalry in many respects and may share some common mechanisms. However, rivalry alternation rate is slower and weaker for PR than BR. The current results illustrate how, in the absence of interocular competition, bistable perception still occurs, but with different dynamics and neural substrates.

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9 - Effect of RORC Inhibition on PD-L1 Expression in Insulin-Producing MIN6 Pancreatic Beta Cells

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Background: RORC, or Retinoic Acid Receptor-Related Orphan Receptor C, is a nuclear receptor and transcription factor crucial for the differentiation and function of Th17 cells¹. Due to its role in immune regulation and its distinctive nuclear ligand-binding domains, which can bind both endogenous and synthetic small ligands, RORC has emerged as a target for drug development in inflammatory and autoimmune conditions¹. Our group has developed novel RORC inhibitors, such as TF-S10. Initial data indicates potential activity in RORC mediated pathways governing inflammation, auto-immunity, and cell growth. Evidence indicates that RORC downregulates the immune signaling pathway Programmed Death Ligand 1 (PD-L1)⁴. Programmed death 1 (PD-1), an immune checkpoint present on activated T and B cells, is crucial for self-tolerance. Preclinical studies show that the interaction with its ligand, PD-L1, inhibits T cell activation, eventually causing their apoptosis, and reducing the severity of autoimmune diseases⁵. The inhibition of PD-1/PD-L1 accelerates the onset of diabetes in NOD mice⁶, whereas the overexpression of PD-L1 in these models prevents it⁷. The expression of PD-L1 is found on the pancreatic islets of people with T1DM, specifically up-regulated in insulin-containing islets and absent in insulin-deficient islets. This further highlights the protective response of PD-1/PD-L1 to inflammation in T1DM⁸. We speculate that RORC may regulate the PD-1/PD-L1 axis in beta cells; however, no literature currently exists demonstrating this relationship in T1DM. This project aims to evaluate the role of RORC in PD-L1 expression and specifically how an RORC inhibitor, like TF-S10, could influence PD-1/PD-L1 expression in MIN6 cells, a murine pancreatic beta cell line. This could reveal RORC inhibitors' potential as protective agents in T1DM by modulating PD-L1 expression.

Methods: Insulin-secreting MIN6 cells are cultured in an FBS-supplemented medium. The cells are then divided into two groups: one receiving no cytokines and one receiving a cocktail of inflammatory cytokines (IL1 β , IFN γ and TNF α) which are an established model of inflammation in T1DM. In the first part of the experiment, an RORC gene knockdown using siRNA (Lipofectamine) will be used. In the second part of the experiment, different doses of TF-S10 will be administered to inhibit RORC. Respective controls are established. PD-L1 expression is measured using real-time quantitative PCR and cell proliferation is measured using Incucyte.

Results: Results of the qPCR and Incucyte will be analysed and presented once obtained.

Conclusions: Future investigations include evaluating the PD-L1 expression on human islet cells and in NOD (non-obese diabetic) mice undergoing the same TF-S10 treatment. This will help us determine its potential therapeutic benefits and translational applicability.

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10 - Pharmacokinetic exploratory assessment of antimicrobials for treatment of acute exacerbations of Chronic Obstructive Pulmonary Disease in hospitalized patients colonized with *Pseudomonas aeruginosa*

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Introduction: Chronic obstructive pulmonary disease (COPD) is a respiratory disorder with persistent airflow obstruction, affecting approximately 392 million people worldwide. The disease features acute exacerbations of COPD (AECOPD), marked by increases in respiratory symptoms often triggered by infections. *Pseudomonas aeruginosa* colonization raises the risk of exacerbation and death in patients with COPD. Treatment for those colonized with this pathogen involves anti-pseudomonal antibiotics. The susceptibility profile of *P. aeruginosa* can change over time due to prior antibiotic exposure. Given that sputum cultures are often unavailable at the time of exacerbation and increasing antimicrobial resistance (AMR), physicians rely on clinical judgment, leading to uncertainty about antibiotic efficacy. Studies suggest that current anti-pseudomonal antimicrobials do not reduce hospital stays, and rising AMR complicates the finding of effective treatments as the minimum inhibitory concentration (MIC) continues to increase. Our primary objective is to assess antimicrobial serum concentrations in patients with AECOPD involving *P. aeruginosa* to determine the proportion of patients with optimal serum concentrations. Our secondary objective is to develop a population-based pharmacokinetic/ pharmacodynamic (PK/PD) model for the antimicrobials studied and to determine the association between suboptimal serum concentrations and treatment failure

Material and Methods: This study aims to enroll at least 30 patients, with a minimum of 12 patients per main antibiotic (piperacillin-tazobactam, ceftazidime, ciprofloxacin, meropenem) under investigation. To be eligible, patients must have an AECOPD classified as 'moderate' (GOLD 2), 'severe' (GOLD 3), or 'very severe' (GOLD 4) chronic airflow obstruction. Additionally, patients must be colonized with *P. aeruginosa* and must be treated with one or more of the targeted antimicrobials: piperacillin-tazobactam, ceftazidime, cefepime, ceftobiprole, meropenem, ciprofloxacin or ceftolozane-tazobactam. Each participant will provide two sputum samples: one at the start of antibiotic treatment, and another once steady state is reached (3-7 days). These samples will be analyzed to assess the susceptibility of *P. aeruginosa* and to measure the MICs of the antibiotics. Additionally, participants will undergo three blood samples (4.5 cc each) in a single day after reaching steady state. These will be collected one hour after the end of antibiotic infusion (i.e. at 0% of the dosing interval), at 50% of the dosing interval, and just before the next dose (i.e. at 100% of the dosing interval). From the blood samples, serum concentrations of the antibiotics will be determined.

Results: The primary endpoints include the variability in peak, trough, and mid-dosing interval concentrations of the antibiotics, as well as the proportion of patients achieving the PK/PD targets. For beta-lactams and carbapenems, the target is achieving 50% of the dosing interval above the MIC. For ciprofloxacin, the target is an area under the curve to MIC ratio greater than 125. The secondary endpoint is to develop a PK/PD model for the antimicrobials studied.

Conclusions: This study seeks to evaluate current prescribing practices for patients AECOPD involving *P. aeruginosa*. By analyzing serum concentrations and developing a PK/PD model, we aim to identify treatment gaps and offer insights for optimizing therapy and patient monitoring.

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11 - Characterization of cell type-specific extracellular metabolites using a novel patient-derived esophageal adenocarcinoma-on-a-chip platform

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Introduction: To date, esophageal adenocarcinomas (EACs) rank among those with the lowest 5-year survival rates, at around 16% in Canada. This alarming statistic is due to the lack of accurate preclinical models, biomarkers for appropriate treatment, and, most importantly, clinical solutions for inter and intra-patient heterogeneity. Systemic cytotoxic peri-operative (4 cycles prior to and 4 cycles following surgical resection) docetaxel-based triplet chemotherapy is currently the only standard of care. In addition, the mechanisms of tumor-stromal metabolic interactions in the tumor microenvironment are dynamic and complex, contributing to transcriptomic, proteomic, and metabolic reprogramming crucial for the development, proliferation, survival, and drug resistance of cancer and its associated stroma. However, metabolic reprogramming in EAC is still poorly understood. Our goal is to identify metabolic vulnerabilities in the EAC microenvironment and to develop strategies to target these to overcome chemoresistance.

Methods: To establish an approach simulating the cellular and physiological environment of the human esophagus in vitro, the Ferri Lab adapted a state-of-the-art organ-on-a-chip (Organ-Chip) technology (Emulate Inc.). This model comprises a polymer-based platform with two parallel channels separated by a porous membrane and can provide cells with a physiologically relevant unidirectional flow of nutrients. The lab has successfully established a novel, patient-specific EAC-Chip platform that creates a tumor-stroma interface and demonstrates in vivo-like EAC clinical mimicry for 12 to 15 days post-seeding under nutrient flow. The upper channel of the EAC-Chip is lined with epithelial tumor cells from chemoresistant patient-derived organoids, and the lower channel is lined with patient-derived and -matched cancer-associated fibroblasts (CAFs). Though metabolites can be identified by analyzing patient sera, the cellular origins of these metabolites are difficult to ascertain. The exclusive design of the chip allows us to separately sample nutrient media before and after exposure to patient-matched tumors and CAFs. We conducted targeted metabolomics analyses focused on central carbon metabolism using both GC-MS and LC-MS/MS methodologies with epithelial and fibroblast-exposed effluents from the

EAC-Chip to precisely characterize extracellular metabolites and the uptake and secretion patterns of biogenic amines and glycolysis/TCA cycle intermediates for each cell type, as well as to identify either biomarkers or targetable proteins involved in cancer-associated metabolic reprogramming.

Results: Preliminary data revealed strikingly different yet complementary metabolic activities of tumors and CAFs. The results indicated the dependency of tumor cells on the Warburg effect (elevated uptake of thymidine, followed by selective utilization of intermediates in glycolysis and the lack of TCA cycle intermediates). Most notably, we detected high levels of uric and lactic acid excretion specifically from CAFs, which can have a pro-oxidative effect and modify cellular metabolism to support tumor growth. Similarly, elevated uptake of taurine and hypotaurine by CAFs and elevated excretion by tumor cells may also signal a response from CAFs to combat oxidative stress.

Conclusions: The EAC-Chip can accurately recapitulate clinically relevant metabolic activity of the tumor microenvironment in EACs, potentially unveiling EAC biomarkers and aiding in developing strategies to target cancer metabolism for precision oncology.

12 - T Cell-Monocyte Complexes and Related Immune Cell Perturbations in Preeclampsia: A Scoping Review

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Introduction: Preeclampsia is a pregnancy disorder characterized by high blood pressure and end-organ damage. Affecting up to 8% of pregnancies, it can lead to severe health complications for both the mother and fetus. Despite numerous risk factors associated with the development of preeclampsia, including obesity, chronic hypertension, diabetes, among others, the definitive cause of preeclampsia remains elusive. The immune system plays a crucial role in the pathophysiology of preeclampsia, yet its exact involvement in preeclampsia development has not been fully elucidated. Recently, studies have identified increased numbers of CD3⁺ CD14⁺ T-cell/monocyte complexes in the blood of individuals with hypertension, demonstrating a significant association between these T-cell/monocyte complexes and hypertensive disorders. These complexes could potentially provide insight into the inflammatory nature of preeclampsia. Thus, this study aims to perform a scoping review of the literature to gather available clinical information on T-cells, monocytes and their interactions in the context of preeclampsia.

Materials and Methods: A literature search was conducted using PubMed and Medline databases to identify studies published since 2010. The search strategy included terms such as “preeclampsia,” “T cells,” “monocytes,” “inflammation,” hypertensive disorders of pregnancy,” “Th1/Th2,” and related terms to capture all relevant studies. Studies were included if they presented primary clinical research identifying T-cell and/or monocyte populations from the blood of individuals with preeclampsia. Data extraction involved systematically reviewing selected studies and recording the following information: study characteristics, T-cell and monocyte populations, methods of identification, interactions and complexes, inflammatory markers, and key findings. A table was then created to organize and highlight the different types of T-cells and monocytes, linking them to the respective studies and synthesizing key findings.

Relevance/Conclusion: This literature review serves as a preliminary exploration to identify key T-cell and monocyte subsets involved in preeclampsia. Results from this study will provide a framework for future targeted analysis of blood samples to identify potential T-cell monocyte complexes involved in preeclampsia. Thus, it will inform the design of our future original study using the samples of our early Prediction of preeclampsia Using arterial Stiffness in high-risk pregnancies; a multinational study (PULSE) study. This will enable a more direct and conclusive examination of the key factors perturbing the immune system in individuals with preeclampsia, which may inform future research on the prediction, diagnosis and treatment of this devastating disorder.

Source of Funding: This study was funded by the Canadian Institutes for Health Research (Project# 168918), Fonds de Recherche du Québec - Santé (Project# 25045), Heart and Stroke Foundation of Canada (Project# 000437)

13 - CRISPR Cas9 mediated knock-in of landing pad into genomic safe harbour site

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Introduction: Viral-mediated genomic insertion is commonly used to introduce foreign genes into cells. However, random insertion can disrupt essential genes or occur in silenced loci, affect the accuracy of gene studies. Aznauryan et al. identified Roci1, a Human genomic safe harbor site (GSHs) on chromosome 1, distant from known genes and regulatory elements, ensuring stable expression without disrupting the cell transcriptome. Bxb1 recombinase-mediated cassette exchange (RMCE) system utilizes bxb1 recombinase from bacteriophage, it combines attP to attB attachment site in pre-engineered landing pad destination, creating half-sites and exchange vector DNA into host genome. This method is advantaged over lentivirus and transposase because of its precise and unidirectional integration, less prone to undesired mutagenesis, and predictable expression characteristics. Evolved bxb1 (eebxb1) has 3 amino acid mutations compared to wild type bxb1, results in higher integration efficiencies. We aim to develop an efficient and accurate method for delivering genes to the Roci1 site using bxb1 RMCE system and explore its potential for CRISPR genome screening.

Material and Method: We co-transfected 293 cells with a puromycin-Cas9-sgRNA plasmid against Roci1 site and an RCME donor landing pad plasmid containing a blue fluorescent protein (BFP) flanked by attP sites. After puromycin selection and flow cytometry sorting for blue cells, we transfected these cells with a plasmid contained promoter-less red fluorescent protein (RFP) flanked by attB sites and a Bxb1 recombinases. The switch from BFP to RFP expression indicates successful exchange of the transgene into RMCE landing pad in cell genome. PCR is used to confirm the integration of landing pad at the Roci1 site.

Results: We cultured sorted 293 blue cells. The constant expression of BFP indicated successful integration of the RMCE landing pad into the genome by Cas9-Roci1 sgRNA plasmids. Integration site will be confirmed by PCR once single clone of blue cells are obtained. The BFP-to-RFP switch was tested with Bxb1 or eebxb1 RFP plasmids. Single and double positive red fluorescence expression detected by flow cytometry indicates Bxb1 recombinase could exchange RFP into the RMCE landing pad via attB-attP recombination, with efficiency of 8-9%.

Conclusion: Precise, one-time insertion of gene into a safe human harbor site ensures accurate results when screening specific gene functions, pathways, and biological mechanisms. Once site of integration is tested and stable Roci1 cell line is established, different genes of interest can be cloned into the RFP/Bxb1 plasmid, transfecting these plasmids will facilitate easy genome screening.

14 - Novel therapeutics for heterotopic ossification (HO) induced by polytraumatic spinal cord injury (SCI)

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Background: Heterotopic ossification (HO) is a condition where bone forms abnormally in soft tissues such as muscles and tendons. HO is common after spinal cord injuries (SCI) and can also occur post-surgery, triggered by an inflammatory response that activates bone growth pathways. HO symptoms, such as restricted mobility and pain, significantly affect patient recovery and quality of life. Current treatments, including physical therapy and surgical resection, are limited and often ineffective, with surgery being invasive and prone to incomplete removal, leading to recurrent issues. This study aims to determine whether inhibiting specific neuropeptides can prevent HO development.

Methods: Twenty 10-week-old C57BL/6J female mice were subjected to a spinal cord transection to induce an SCI at T9-T10, followed by a musculotendinous injury (MTI) by crushing the left quadriceps muscle and tendon. The right limbs were left intact to serve as controls. The mice were divided into four treatment groups to receive injections of either calcitonin gene-related peptide inhibitor (Olcegepant, 1mg/kg), substance P inhibitor (Aprepitant, 10mg/kg), a combination of anti-CGRP and anti-SP, or vehicle (5% DMSO + 95% normal saline).

The mice were euthanized and hindlimb samples were surgically extracted at four weeks post-operatively and analyzed using micro-computed tomography (micro-CT). Tissue sections were then embedded in methyl methacrylate (MMA) or paraffin for histological analysis. Histological staining included Von Kossa for mineralization, alkaline phosphatase (ALP) staining for osteoblast activity tartrate-resistant acid phosphatase (TRAP) staining for osteoclast activity and safranin O (SO) for chondrocyte activity. Immunofluorescence was performed to confirm the presence of osteoblasts and macrophages.

Results: Four mice were excluded from the study due to wound dehiscence at MTI site: two from the anti-CGRP group, one from the combination group, and one from the vehicle group. 3D micro-CT image reconstructions revealed ectopic mineralization in tissue sections from all four treatment groups. Compared to the vehicle group, the anti-CGRP group exhibited similar levels of mineralization. Mice treated with a combination of anti-CGRP, and anti-SP showed similar to slightly higher levels of mineralization. However, the group treated with anti-SP alone demonstrated less mineralization. The presence of ectopic mineralization observed on micro-CT was confirmed with Von Kossa staining. Additionally, ALP and TRAP staining indicated osteoblast and osteoclast activity, respectively, in all four treatment groups.

Conclusions: Our findings suggest that the anti-SP injection reduces mineralization, thus targeting specific neuropeptides could be an effective strategy for reducing heterotopic ossification (HO) in patients with spinal cord injuries (SCI). A larger sample would be necessary to confirm these results.

Source of funding: Department of Medicine, MUHC; Faculty of Medicine and Health Sciences; North American Spine Society; AO Spine North America; AO Spine.

15 - Quantifying Radiation-Induced DNA Damage via Track-Structure Simulations in a Nuclear DNA Model

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The cellular response to ionizing radiation is primarily a reaction to DNA damage induction. To study this, the Kildea Lab employs a Monte Carlo simulation pipeline to predict DNA damage caused by high-energy particles prior to carrying out *in vitro* experiments. [1] However, the lab's current pipeline does not fully account for biological outcomes. To address this, in this summer project, we are incorporating into the pipeline an algorithm called "Mechanistic DNA Repair and Survival" (MEDRAS) [2] and using it to assess single-cell viability and the occurrence of lethal chromosome aberrations and double-strand breaks following radiation-induced DNA damage.

To date, we have completed the main software development work and subjected the simulated DNA model to various doses from monoenergetic proton sources of 0.88 MeV, 1.38 MeV, and 5.04 MeV energies. We found that the average count of double-strand breaks across 100 simulations was 63.06/Gy, 53.84/Gy, and 39.99/Gy for each proton source, respectively. Correspondingly, the average count of chromosome aberrations was 0.829/Gy, 0.508/Gy, and 0.174/Gy for each source, showing a reduction in DNA damage as proton energy increases. This is consistent with the well-known reduction in linear-energy transfer (LET) with increasing energy for a given radiation type.

By predicting a testable DNA damage trend as a function of energy, this *in silico* work is a stepping stone towards the Kildea lab's goal of examining radiation-induced DNA damage *in vitro* using single-cell whole-genome DNA sequencing.

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16 - Exploring the Determinants of Excess Weight Gain in Women with Gestational Diabetes: A Focus on Demographics, Food preparation skills, and Eating Habits

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Introduction: Many women with gestational diabetes (GD) gain weight above the recommended guidelines, increasing risks for maternal and offspring complications. Eating habits are an important driver of weight gain. Beyond dietary composition, there has been limited examination of other food related behaviours, such as cooking skills, eating alone, and eating out or ordering in. We hypothesized that these factors are drivers of both prepregnancy weight status and gestational weight gain in women with GD.

Material and Methods: I am conducting a secondary analysis of data from the Active Patient GDM trial, which assessed the feasibility of various self-management strategies to help GDM-affected women improve their outcomes. I am specifically focusing on the food-related behaviours highlighted above (n=215). I am generating descriptive statistics (mean, standard deviation, number, percent, as applicable) of food-related behaviours, demographic factors, and prepregnancy weight status. I am stratifying these by categories of total gestational weight gain (below, within, and above prepregnancy weight category specific guidelines). I will use logistic regression to evaluate associations of these factors with on-target weight change, accounting for trial arm.

Results: The preliminary results demonstrated an ethnically diverse cohort of participant, who identified as White (31%), South Asian (16%), East Asian (12%), West Asian (12%), Southeast Asian (11%), or Other. Additionally, most women had a university degree (77%) and worked full time (72%). In terms of eating habits, nearly 40% spent more than 5 times a week eating their main course and/or snacks in front of a screen. The percentages of participants who ate their breakfast, dinner, and lunch at home were 91%, 76%, and 94%, respectively. Moreover, 56%, 48%, and 91% ate their breakfast, lunch, and dinner with family. Remarkably, around 40% ate their breakfast and lunch with nobody, yet the percentage of participants with no meal companion reduced to only 8% for dinner. Over 60% cook their main meals themselves. Furthermore, while over 80% purchase their food supplies from the grocery stores, less than 15% source their meals from restaurants or cafeterias. The participants weighed 56.7 (SD 12.0) kg on average at 18 years of age; 61% were normal weight, and only 3% were obese. Nonetheless, the average weight before the index pregnancy, was 71.1 (SD 18.3) kg, with 42% being normal weight and 23% obese.

Conclusions: These preliminary findings indicate a diverse group of educated working parents to be with important levels of screen time during food consumption. Surprisingly, despite the participants screen-oriented meal practices, a significant percentage still eat at home and with family. The results will thus provide valuable information about lifestyle factors that contribute to excess gestational weight gain.

Source of Funding: This Summer Research Project is funded through the Dr. Harry I. Cramer Research Scholarship.

17 - An Evaluation of the Economic and Resource Burden of COPD and of Exacerbations of COPD (ECOPD) on the COPD Clinic and MUHC

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Introduction: Chronic obstructive pulmonary disease (COPD) is a common lung disease characterized by breathlessness, exercise intolerance, lung function decline and sudden 'lung attack' episodes known as 'exacerbations.' Exacerbations of COPD (ECOPD) are one of the top causes of hospital admissions amongst adult chronic diseases. COPD is the third-leading cause of death globally and carries a significant burden on both patients and healthcare systems. There is an increased interest in remote monitoring techniques using wearable devices capable of measuring multidimensional parameters, such as vital signs, activity and sleep data which potentially reduce the burden of in-person monitoring in clinics, provide a more efficient monitoring approach that allows for early intervention and minimize the need for hospitalization. Implementing remote monitoring platforms requires significant financial investment. Therefore, it is critical to examine the cost-benefit economic potential of these clinical monitoring platforms by comparing them to the costs associated with traditional in-person monitoring. The objective of this study is to analyse the healthcare resources utilized for each patient with COPD who seeks medical assistance due to an ECOPD.

Material and Methods: A retrospective chart review of 21 patients with COPD recruited in our prior study of determining feasibility, functionality and user experience of wearable technologies for monitoring ECOPD will be comprehensively conducted to determine resource utilization including hospitalizations period, emergency room visits, physician services, drugs, and all diagnostic tests (e.g., lab tests, imaging). Costs for outpatient investigations including blood tests and diagnostic imaging will be obtained from the Quebec fee schedule. In addition, Régie de l'assurance maladie du Québec (RAMQ) reimbursement rates in effect will be used to determine drug and medication costs. Costs for any laboratory testing done in-house, day-hospital visits and hospitalizations will be obtained from the department of finance at the MUHC. To estimate overall costs per patient, we will use the frequency occurrence of specific activities and their corresponding costs. We will describe associated costs using both mean (standard deviation) and median (IQR).

Results: The retrospective chart review of 21 patients with COPD will clearly indicate that, on average, each patient utilizes specific treatments and resources that incur significant costs. Upon concluding this study, an informed estimate of the per-unit economic cost for each individual patient with COPD will be determined.

Conclusions: This study aims to analyse the healthcare resource utilization by patients with COPD who seeks medical assistance due to an ECOPD. Determining the economic cost of traditional in-person monitoring will support the potential cost-benefit of implementing remote monitoring platforms for managing patients with COPD.

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18 - PXGS: a Poly-Transgene Expression System based on Mutually Exclusive Alternate Splicing

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The simultaneous expression of multiple genes within an animal remains a significant challenge in genetic research, despite its potential utility across disciplines. Traditionally, each transgene is generated in separate individuals, requiring multiple crosses to express multiple transgenes, or a completely different approach to achieve poly-transgene expression. Our lab has invented a system that leverages the mutually exclusive alternate splicing of the *Down syndrome cell adhesion molecule (Dscam)* gene to allow for conditional expression of 12 transgenes at a time in *Drosophila melanogaster*.

Here, I tested this poly-transgene expression system (PXGS) in *Drosophila melanogaster* S2 cell lines. I inserted six *iLux2* bioluminescence genes within PXGS through multiple rounds of molecular assembly. This process involved assembling the six target genes into two DNA fragments, purifying the resultant plasmids and integrating them into the destination vector. GenoDig.org, an advanced software for molecular assembly, was instrumental in the process. Gibson assembly was used to combine all of the DNA fragments into a single plasmid. My results demonstrate that PXGS can achieve robust poly-transgene expression, thus providing a versatile platform for synthetic biology.

19 - Varicella zoster virus serology in pediatric patients treated with biologic therapies

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Varicella-zoster virus (VZV) is a highly infectious virus and the causative agent of chickenpox during primary infection, and shingles following reactivation, often in immunocompromised hosts. There are 2 types of vaccines available for VZV; a live attenuated contraindicated for immunocompromised individuals and a particulate vaccine indicated for the elderly and immunocompromised adults. The vaccination status and the presence of seroconversion to VZV is not routinely evaluated in children undergoing biologic treatment. Yet, these patients may have increased susceptibility to VZV infections. This study aims to establish VZV serology in pediatric patients at the start of their biologic therapies and follow VZV antibody levels during and after completion of biologics. The patient cohort is part of the Centre Transdisciplinaire de Thérapies Biologiques (CTTB) biobank and registry.

Vaccination status and past serology of the patients were compiled from the CTTB registry. An in-house enzyme-linked immunosorbent assay (ELISA) for anti-VZV antibody quantification was developed using Oka (vaccine) strain and recombinant (wild type WT) envelope glycoprotein E (gE) antigens. Serum from pediatric patients undergoing Rituximab or Infliximab therapy were/will be analyzed at baseline and 6-months, 1-year and 2-years post start of biological therapy.

Eighteen patients were selected, 7 treated with Rituximab and 11 with Infliximab. Using Oka antigen, 5 patients (28%) were seronegative for VZV; 3/5 of which were not vaccinated and 2/5 received one VZV vaccination. Five different patients (28%) were seronegative to WT virus; 2/5 were never vaccinated, 2/5 had one vaccine and 1/5 had history of both natural infection and vaccination.

Pediatric patients beginning biologic treatment may be at risk of VZV infection. Biologic therapies reduce the ability of patients to respond to infections. Our data highlight the importance of assessing seropositivity in patients and to consider the particulate VZV vaccine (Shingrix®) for these immunocompromised individuals.

20 - DEVELOPMENT OF BIODEGRADABLE AND BIOACTIVE INJECTABLE HYDROGEL FOR IVD REPAIR

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Background: Low back pain (LBP) is primarily due to the degeneration of the intervertebral disc (IVD), particularly the loss of functional nucleus pulposus (NP), which is the gel-like core of the IVD. The NP is essential for disc function and is composed mainly of water, collagens, and proteoglycans, which help maintain disc height through osmotic swelling pressure. Aging reduces NP proteoglycan and water content, leading to extracellular matrix (ECM) degradation, decreased NP cell density, and increased matrix-degrading enzymes, resulting in a stiffer, more fibrotic disc. These changes impair the disc's ability to support nutrient supply and waste removal, limiting its regenerative capacity. To effectively regenerate the IVD and address LBP, cell-based regenerative strategies utilizing hydrogels and mesenchymal stem cells (MSCs) present promising avenues for both immediate and long-term restoration of NP function. In this project, we have functionalized CHAD-peptide conjugated alginate oxide (Alg-O-CHAD) hydrogel as the carrier to deliver mesenchymal stem cells to the disc. In the short term, the Alg-O-CHAD can match native tissue viscoelasticity and restore biomechanical function. In the long term, the encapsulated cells are expected to aid in forming a functional ECM, including type II collagen and aggrecan, crucial for NP function restoration. To enhance NP-like differentiation, NaAlg will be conjugated with cell adhesion ligands derived from chondroadherin protein (CHAD) using maleimide chemistry. The biodegradable Alg-O-CHAD hydrogel could also degrade naturally within the body due to the hydrolysis of the alginate oxide.

Materials and Methods: A 1% aqueous solution of low molecular weight sodium alginate (Alg) was prepared and mixed with a 60% and 100% molar ratio of sodium metaperiodate to make alginate oxide (Alg-O). The resulting Alg-O was then dialyzed and freeze-dried. NMR and FTIR analyses were performed to confirm the presence of the aldehyde group in Alg-O. The Alg-O was then reconstituted in a 1% solution and immobilized with the cysteine-containing CHAD peptide using an N- β -maleimidopropionic acid hydrazide (BMPH) intermediate through maleimide chemistry. NMR and SDS-PAGE analyses will confirm the conjugation of the peptide. Human bone marrow MSCs, expanded in α MEM basal media at Passage 3, will be mixed with the Alg-O-CHAD. The Alg-O-CHAD will be crosslinked to form a gel by mixing with a CaSO₄ slurry. Biocompatibility and protein formation will be evaluated through live/dead assays, histology (Safranin-O staining), and immunofluorescence staining (Type II collagen) after 3 weeks of in vitro culture.

Results: The formation of the alginate oxide was confirmed by FTIR (1735 C=O stretch). The conjugation of the CHAD peptide has been performed but is still to be confirmed by the NMR results. Cell viability and protein formation are still to be determined.

21 - METHYLATION PROFILING IDENTIFIES THREE DISTINCT CLUSTERS OF SMALL CELL CARCINOMA OF THE OVARY HYPERCALCEMIC TYPE (SCCOHT) WITH SPECIFIC MORPHOLOGICAL FEATURES

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Background: Small cell carcinoma of the ovary hypercalcemic type (SCCOHT) is an aggressive type of ovarian cancer predominantly affecting young women. The early onset and high mortality rate of SCCOHT pose significant diagnostic and therapeutic challenges. The underlying genetic and epigenetic mechanisms contributing to SCCOHT are not fully understood, although recent studies have highlighted the importance of SMARCA4 mutations as a key driver of this malignancy. DNA methylation alterations, an epigenetic modification regulating gene expression, has been implicated in various cancers, including SCCOHT. Recent advancements in methylation profiling have provided valuable insights into tumor biology. In this study, we conducted a comprehensive methylation analysis of SCCOHT samples to delineate the epigenetic landscape of this malignancy and find a correlation with histopathological features.

Material and Methods: We retrieved a series of SCCOHT malignancies with available tumors tissue from a multi-centre cohort. The histopathological features of each case were reviewed centrally. DNA extraction for methylation profiling was performed on all cases. We used the Infinium Methylation EPIC v2.0 Beadchip assay (Illumina). Unsupervised clustering and t-SNE algorithms were performed to highlight the different methylation profile among our cohort. Associations between methylation clustering and histopathological features were assessed using chi-squared tests.

Results: We included 25 cases of SCCOHT in our study. Analysis of the methylation profiling identified three distinct clusters. The three clusters were each associated with specific chromatin morphology ($P = 0.04127$) and the presence of rhabdoid cells ($P = 0.06512$). Specifically, Methylation Cluster 3 is predominantly linked to smudged chromatin states. Methylation Cluster 2, on the other hand, shows a higher occurrence of stippled and clear/vesicular chromatin states. Lastly, Methylation Cluster 1 is predominantly associated with the stippled chromatin state, followed by the clear/vesicular state. Methylation cluster 1 is most associated with the presence of rhabdoid cells, followed by the second methylation cluster.

Conclusions: Methylation profiling of SCCOHT has identified three distinct clusters with specific morphological features. The presence of rhabdoid cells predominantly in the first cluster in addition to association between cluster number and chromatin state suggest underlying biological differences. These findings may provide a novel classification framework for SCCOHT as well as a better understanding of the pathogenesis of this aggressive malignancy. Further studies are warranted to determine the diagnostic, prognostic and therapeutic implications of these findings.

22 - Comparison of Derived Parameters from a Commercial Oscillometer to those of a Custom Written Multi-Purpose LabView-Based Engineering Software

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Background: Oscillometry is a pulmonary function test that is gaining popularity in the field of respiratory medicine due to its efficient and noninvasive nature. While all commercial oscillometers measure pressure and flow, how they calculate the derived parameters of interest is variable and results are known to diverge, especially at higher impedances. One proposed solution has been to output raw pressure flow signals only from commercial devices and process them through a standard filtering and modeling software for the calculation of the derived parameters. We sought to do one such pilot study targeting a single oscillometer (tremoFlo C100, Thorasys, Montreal, Canada) as the device to measure pressure and flow and additionally process that data through our own in-house rigorous and well characterized software (LVOsc, University of Szeged, Hungary) to calculate the derived parameters. Given prior evaluations using standardized test loads, we hypothesize that there will be little difference in the derived parameters between the two signal-processing methodologies.

Methods: We performed a retrospective re-analysis of existing data. Pressure and flow data collected from 30 patients in Dr. Dandurand's clinic were included. This data was then inputted into the tremoFlo software to calculate data for the derived parameters of interest, resistance at 5 Hz (R_5), frequency dependence of resistance (R_{5-19}), the reactance at 5 Hz (X_5), resonance frequency F_{res} , and reactance area (A_X). This same pressure and flow data was then also run through LVOsc in order to obtain the same derived parameters. The agreement between tremoFlo and LVOsc will then be evaluated using Bland-Altman plots, intraclass correlation coefficient (ICC) and Cohen's Kappa (CK), which will be performed using JASP. Biometric, lung function and oscillometry data will be expressed as medians and IRQ.

Results: Although we are still in the process of analyzing our data, we anticipate obtaining comparable values of R_5 , R_{5-19} , X_5 , F_{res} and A_X between the commercial tremoFlo software and the novel LVOsc software, which would indicate that tremoFlo accurately reports the derived parameters used to describe lung mechanics. If the results show significant deviation between the outputs of both softwares, further study would be required to determine the origins of such divergences. This would strengthen the argument that all devices should allow for easy outputting of pressure and flow signals for device independent analysis.

Conclusions: The validation of a commercial oscillometry device through a comparative analysis of quality would verify that the oscillometry measures that were collected in clinics are accurately translated into the parameters of interest that are used when evaluating patient lung functions and monitoring for respiratory disease. This would indicate that the past measurements are valid, and that this software can remain a reliable option for clinicians to derive the parameters of interest.

Source of Funding: This project is supported by the Dandurand Lab.

23 - Neural Markers of Consciousness in Brain-Injured Pediatric Patients Exposed to Anesthesia

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Introduction: The Pediatric Intensive Care Unit (PICU) provides critical care to brain-injured children and often uses anesthesia to stabilize patients. These patients suffer from conditions including epilepsy, anoxic injury, traumatic injury, and cerebrovascular disease. Understanding the effects of anesthetics on brain dynamics and levels of consciousness is crucial to optimize patient care and prognosis. Our study explores the electrocortical dynamics of pediatric patients of different ages and etiologies using an electroencephalography (EEG) dataset collected from the McMaster Children's Hospital PICU. We hypothesize that specific EEG features can reliably indicate the depth of anesthesia, level of consciousness and patient outcome.

Methods: The dataset comprises EEG recordings collected from pediatric patients under propofol, midazolam, dexmedetomidine and ketamine anesthesia. The EEG data were formatted into the Brain Imaging Data Structure (BIDS) and preprocessed using Python tools (MNE, Numpy, Pandas, Scipy). Preprocessing included setting the montage, bandpass filtering (0.5-45 Hz), notch filtering (60 Hz and 120 Hz), referencing, Independent Component Analysis (ICA) for artifact removal, epoching, and Auto Reject cleaning. High-power mechanical noise peaks were identified with the power spectrum modelling package FOOOF and removed with a custom IIR notch filter. Remaining noisy channels were identified in Power Spectral Density (PSD) plots of each file, and up to 25% of all channels were removed to improve data quality. The analysis will focus on EEG features such as relative band powers, aperiodic parameters, and criticality measures like Lempel-Ziv complexity, and the Hurst exponent.

Results: Preliminary results show successful noise reduction and improved signal quality post-preprocessing. The McMaster Children's Hospital dataset contained 41 initial participants, 5 of whom were excluded due to noisy data, and 8 omitted due to incomplete EEG recordings. Within the remaining participants, 2.38% of all EEG channels were removed. The mean age of the remaining participants was 9.96 ± 4.95 (range: 0.083 to 17 years). Prognosis is measured with the Glasgow Outcome Scale-Extended (GOSE), an 8-point measure of patient outcome recorded 3 months post-insult. Participants with scores 1-2 have a complete loss of consciousness, whereas participants with scores 3-8 have varying degrees of regained consciousness. Of the 28 remaining participants, 2 have a GOSE < 3, 25 have a GOSE 3-8, and 1 is missing data. Using logistic regression, we will analyze prognosis with two categories: consciousness loss or recovery.

Conclusion: Our study aims to illustrate how EEG features can predict return of consciousness in brain-injured pediatric patients. By identifying EEG patterns linked to different anesthetics, we can understand how levels of consciousness change with environmental factors. These findings highlight the potential of EEG analysis to enhance clinical assessments and prognosis for patients in the PICU.

Source of Funding: This research was supported by the Natural Sciences and Engineering Research Council of Canada (NSERC) Undergraduate Student Research Awards (USRA).

24 - Identifying genetic causes of unexplained familial infertility cases

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Background: Human infertility is a disease defined by the inability to achieve pregnancy after a minimum of 12 months of regular unprotected intercourse. Worldwide, it is estimated that 1 in 6 adults are affected. The causes of infertility are diverse, ranging from sexually transmitted infections to non-communicable diseases. However, approximately 50% of all cases are thought to be caused by a genetic defect. This project's aim was to identify new genetic etiologies of infertility in two familial cases that have remained unexplained under the hypothesis of a common genetic defect responsible for the phenotype of the affected members.

Methods: Whole-exome sequencing (WES) was performed on genomic DNA (gDNA) extracted from the blood of patients referred for infertility. The WES data were filtered to rule out common variants and those in genes unrelated to human reproduction. This filtering was separately done for both the recessive and dominant modes of transmission. The pathogenicity of selected variants was predicted according to the American College of Medical Genetics (ACMG) guidelines to rule out the likely benign ones. A DNA fragment containing the selected variants was amplified by PCR using the patient and their family members' gDNA, and then sent for Sanger sequencing to validate the variants and segregate them throughout the family.

Results: Case 1 consists of an affected brother and sister with a history of infertility and positive parental consanguinity. The female's history includes two years of primary infertility, low levels of Anti-Müllerian Hormone (AMH), and two very early miscarriages. Her partner's semen parameters are normal, and the couple both have normal karyotypes. The male patient presented with 10 years of primary infertility, azoospermia and a normal karyotype. For this family, WES was performed on both affected siblings and their two parents. Analysis of the four exomes independently revealed a *de novo* heterozygous variant in *Wnt4* in the male that is predicted to be deleterious by various prediction softwares. WNT4 plays a role in male and female sexual development and therefore, this variant is a promising candidate that may explain the male's phenotype.

Case 2 consists of three affected sisters from consanguineous parents. Their partners all have normal semen parameters and the three women have been suffering from infertility for 5 to 17 years. Two of the sisters have failed intracytoplasmic sperm injection (ICSI) trials. Previous analyses performed by members of the Slim lab have failed to identify common genetic variants in the recessive mode in the three sisters that could explain their phenotypes, especially since the failed ICSI trial in two of the sisters suggest a germline defect. Analysis of this case, including variants only found in one of the sisters' and both the recessive and dominant modes of transmission, is ongoing and will be presented at the research day.

Conclusions: The goal of this work is to add onto the growing research in the field of infertility genetics. If promising candidate variants are identified, functional assays should be considered in the future to investigate the molecular mechanisms causing the disease phenotypes.

25 - Safeguarding the Vulnerable: Measles Vaccination and Seroprotection in Immunocompromised Pediatric Patients on Biologic Therapies

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Background: Vaccination status and seroprotection against measles in immunocompromised pediatric patients undergoing biologic therapies is a critical concern. These children are at heightened risk for severe complications from measles due to compromised immune systems. Proper seroprotection for this disease is essential to safeguarding their health and preventing outbreaks in vulnerable populations.

This study aims to establish seroprevalence in an immunocompromised pediatric cohort to identify patients unprotected against measles and determine if there is a correlation between biologic used, underlying disease, and seroprotection to measles infection. The cohort is derived from the established Centre Transdisciplinaire Therapeutique Biologique (CTTB) biobank and registry.

Methods: We examined the established CTTB biobank for patients receiving biologics. We evaluated vaccination status prior to start of therapies and examined whether measles serology was evaluated. Using banked serum samples, we are evaluating measles protection using serum antibody levels by ELISA and the sensitive Plaque Reduction Neutralization test (PRNT).

Results: The pediatric CTTB cohort (N=141) are undergoing treatment with biologic therapies including infliximab, and Rituximab. Of the 141 children, 84(69%) received both recommended doses of the vaccine, 24(20%) received only one dose and 13(11%) patients were never vaccinated. Vaccination status was unknown for 20(16.5%) patients. Prior to start of biologic therapy, measles serology assessed in 78% of the cohort revealed that 89(81%) patients were seropositive, 5(4%) patients were in the equivocal range and, importantly, 16(15%) patients were seronegative. Studies are ongoing to determine if these children maintain protection while on treatment.

Conclusions: Childhood vaccine immunization is essential for patients receiving biologic therapies as these are vulnerable, immunocompromised patients. Our findings show significant seronegativity in this cohort. Given recent outbreaks of measles in Canada (77 cases from 2024), these patients are vulnerable to infection and high-risk of morbidity. Establishing pretreatment protocols and ensuring vaccine coverage is essential to protect this vulnerable population going forward.

26 - Optimizing Antenna Distribution for High-Quality Microwave Radar-Based Imaging in Breast Cancer Detection

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Microwave radar-based imaging has emerged as a promising technique for non-invasive medical diagnostics. Notably, this technique has been extensively researched because it does not involve ionizing radiation, avoids the need for breast compression, and relies on relatively inexpensive technology. For other medical imaging technologies, concerns persist regarding health risks associated with regular and repeated ionizing radiation exposure from X-ray in CT (Computed Tomography) and the high expense and bulkiness from MRI (Magnetic Resonance Imaging). This study aims to develop a novel approach for breast tumor detection using microwave radar-based imaging technique.

As a proof of concept, we began with modeling cylindrical homogeneous phantoms, establishing a fundamental understanding of electromagnetic interactions. These initial models are simplified, consisting of a single layer of skin surrounding fat, with a single tumor target embedded within the fat. We then replace fat with gland and vary the number of tumors and their size. The objective is to identify the optimal number and position of antennas distributed around the phantom to obtain high-quality images. Different distributions of antennas were tested for data acquisition, in which patch antennas resonating at 3 GHz were adopted: 4, 6, 8 and 12-antenna setups are placed around the cylindrical model to collect S-parameters. The simulations were performed in HFSS (High Frequency Structural Simulator) and processed on Compute Canada's supercomputer, enabling the efficient handling of complex electromagnetic designs. Leveraging HFSS and Compute Canada's supercomputer, we seek to optimize the simulation workflow to obtain accurate results. The acquired S-parameters were then input into the Microwave Radar-based Imaging Toolbox (MERIT) algorithm to generate medical images. The imaging process involved emitting microwave signals, capturing the reflected signals, and processing these reflections to generate high-resolution images. In these images, we were able to determine specific information about the tumors, including their size, location, and other relevant characteristics.

Our findings indicate that our microwave radar-based imaging technique can effectively detect the presence of tumor in cylindrical homogenous body phantoms with our 8 and 12-antenna arrays. The computational efficiency provided by Compute Canada's supercomputer was crucial in managing large datasets and complex simulations, significantly reducing processing time. The MERIT algorithm has produced detailed microwave images with minimal artifacts and high clarity, providing a proof of concept and highlighting its strong potential for clinical application.

In conclusion, this research confirms the potential of microwave radar-based imaging for clinical applications such as breast tumor screening, stroke detection and bladder state monitoring. The integration of HFSS for modeling and high-performance computing for simulation, together with MERIT imaging algorithm, has resulted in a reliable and accurate imaging technique. Future work will include further variations in tumor size and position within cylindrical homogeneous phantoms, along with testing different antenna distributions, followed by simulations on realistic human models. Additionally, we plan to fabricate human models using a 3D printer and conduct measurements using a portable vector network analyzer and custom wearable antennas.

27 - Identifying Neocortical Layers with Histology

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Background: Neuronal connectivity dictates circuit function in the brain. The neocortex has classically been described as a layered structure, and neurons in each layer form specific connectivity motifs within as well as across layers. To understand cortical computations, we thus need a standardized way to characterize neocortical layers. Methods relying on molecular markers for each layer are commonly used to identify cortical layers. However, layers are not well defined and bleed into each other, which necessitates labeling multiple layers simultaneously. With immunohistochemistry, this is often not possible as many antibodies are made in the same host species and have the same isotype. Therefore, we aimed to develop a standardized approach to delineate neocortical layer boundaries while minimizing caveats.

Methods: We characterized layers in postnatal day 18-26 Emx1^{Cre/Cre} mice, which correspond to the age range and strain for our acute slice experiments for connectivity characterization. We prepared 20-µm-thick paraformaldehyde-fixed frozen brain tissue sections containing multiple neocortical regions. To label cortical layers, we used antibodies against Calbindin D28K (layer 2/3), RORB (layer 4), ETV1 (layer 5), and FOXP2 (layer 6), with donkey anti-rabbit Alexa Fluor 647 as the secondary antibody. We additionally used NeuroTrace Blue (fluorescent Nissl) to counterstain neurons and glia. Mounted sections were imaged with a Zeiss LSM 780 confocal microscope.

Results: Although antibodies stained the appropriate layers, intensity varied across samples and background was high. However, Nissl stained consistently across samples, which allowed us to approximate layer boundaries based on cell density and size. To evaluate Nissl further, we counterstained 300-micron acute brain slices from our acute slice experiments with NeuroTrace Blue. Confocal imaging revealed that fluorescent Nissl staining intensity was not lower in the acute slices, a finding that had not been previously documented in the literature.

Conclusions and Future Directions: We highlight here the importance of standardized neocortical layer identification. Our findings suggest that fluorescent Nissl can be used to accurately identify neocortical layers even in acute slices. Although this approach streamlines our workflow, it still leads to potential experimenter variability in delineating layers. Layer identification using machine learning would circumvent this issue.

Source of funding: CFI, CIHR, NSERC, and FRQS.

28 - Impact of Music Therapy during Targeted Neonatal Echocardiography - A Survey of Neonatal Healthcare Professionals

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Keywords: music therapy, echocardiography, patient comfort, NICU

Background: The neonatal intensive care unit (NICU) is often a stressful environment for newborns and their families. Interventions during routine procedures can help alleviate this stress. Music therapy, for instance, has been shown to improve stress levels, heart and respiratory rates, and oral feeding volumes in preterm infants, while also reducing anxiety in mothers. As such, since 2018, healthcare professionals at the Montreal Children's Hospital (MCH) NICU have been advised to supplement bedside echocardiography with music therapy and a range of other practices.

Purpose: To determine healthcare professionals' perspectives on the impact of certain interventions on patient comfort during targeted neonatal echocardiography (TNE).

Methods: A survey was sent to nurses, neonatal nurse practitioners (NNPs), neonatology fellows, neonatologists, imaging technologists and respiratory therapists working at the MCH NICU, as well as to the NeoCardioLab research personnel, via email and an internet group for the neonatal division. Consent was obtained for every respondent. Responses were collected over four weeks and anonymized. Statistical analyses were performed using RStudio.

Results: Of the 110 respondents, 93 (84.54%) were female, 71 (64.55%) were non-NNP nurses and the mean age was 38 years (SD: 10.23). The majority (n=77; 70%) felt that tests like TNE generally disturb the infant. Ultrasounds and echocardiography scans in general were thought to increase the baby's oxygen needs (50%), sensitivity to manipulation (57%), lability (67%) and risk of hypothermia (75%), as well as alter parental stress levels (54%). The most valued comfort measures during TNE were warm gel (85%), bundling (80%), a focused exam of 30 minutes or less (80%), a dark room (75%), closed isolette doors (75%) and playing music (59%), while less emphasized were keeping parents at bedside (35%) and the type of professional performing the scan (35%). Music during TNE was thought to calm the baby (73%), parents (44%) and sonographer (39%), with only 3%, 3% and 5% of respondents believing the converse, respectively. Regarding the use of music to comfort patients during TNE, most preferred recorded music (53%), followed by live music (10%) and music from a mobile next to the crib (6%), with some favouring no music (6%) or having no opinion on the matter (25%). Finally, respondents most frequently rated warm gel (73%), closed isolette doors (64%), a focused exam (64%) and bundling (63%) as 'very important' in ensuring infant comfort during TNE.

Conclusion: Healthcare workers generally agree that scans can disturb newborns, but interventions like warm gel, closed isolette doors, a focused exam and bundling may enhance patient comfort. While not considered the most crucial intervention, music therapy was recognized as effective in alleviating stress for the patient, family and sonographer, with most respondents supporting its use.

29 - A single-center observational study to assess the pharmacokinetic parameters of beta-lactams and fluoroquinolones in patients 75 and over

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Background: Antimicrobial doses are determined in healthy subjects and validated in selected populations enrolled in clinical studies. However, specific patient groups are usually not included despite having different physiologic parameters and disease states that modify drug pharmacokinetics. In older patients, administration of standard adult doses could expose them to supratherapeutic antibiotic concentrations putting them at risk of adverse events, such as nephrotoxicity and neurotoxicity. (1) Many factors increase the risk of adverse drug events in elderly patients, notably polypharmacy, reduced muscle-mass, the greater prevalence of comorbidities as well as a decrease in renal function. (2, 3) This study targets hospitalized older patients (≥ 75 years old) who are prescribed ciprofloxacin and/or piperacillin-tazobactam. This study seeks to evaluate if the standard doses prescribed to older patients result in effective and safe concentrations. We believe that there is significant variability in antibiotic concentrations in older adults when dosing empirically, which may lead to a higher incidence of dose-related toxicities in this population. The primary objective is to characterize the variability of serum concentrations of the target antimicrobials. In addition, the secondary objectives are to evaluate PK/PD target attainment for each antimicrobial, develop a pk/pd model for dose optimisation and documentation of adverse events possibly related to antibiotic exposure.

Methods: This study includes 12 patients per antibiotic group, totaling 24 patients. Each patient undergoes three blood draws (3 cc each) once the medication's steady state is reached. Blood samples are collected one hour after the end of the infusion (peak), at the mid-point of the dosing interval and 30 minutes before the next dose administration. High Performance Liquid Chromatography (HPLC) is used to determine serum concentration of antibiotics. The results are used to calculate pharmacokinetic parameters for each patient according to first-order methods. Additionally, collective patient results are used to create a population model.

Results: The primary endpoints consist of 1) evaluating the variability of peak, trough, and mid-dosing interval concentrations; 2) the proportions of patients achieving PK/PD target according to suspected pathogen. For beta-lactams, the target is $50\% T > MIC$, and for ciprofloxacin, the target is $AUC/MIC > 125$; 3) Adverse events related to antibiotic exposure are identified as part of usual standard care by the health care team. Preliminary results show

Conclusion: This study seeks to demonstrate that older patients are subject to non-optimal dosing regimens. By analyzing serum concentrations and creating a population model, we intend to characterize the limitations of the current standard for antimicrobial therapy in older patients. In addition, pk/pd model would allow for the development of a new optimization approach with respect to ciprofloxacin and piperacillin-tazobactam treatments.

Source of Funding: Canadian Society of Hospital Pharmacists Foundation and University of Montreal

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30 - Epigenetic Landscape of Small Cell Carcinoma of the Ovary Hypercalcemic Type (SCCOHT): DNA Methylation Profiling and Bioinformatics Analyses

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Background: Small cell carcinoma of the ovary hypercalcemic type (SCCOHT) is a rare and aggressive ovarian cancer that predominantly affects young women. The early onset and high mortality rate of SCCOHT present significant diagnostic and therapeutic challenges. Recent studies have identified SMARCA4 mutations, a crucial gene in the chromatin remodeling SWI/SNF complex, as key drivers of SCCOHT pathology. DNA methylation, an epigenetic modification that regulates gene expression, has been implicated in various cancers, including SCCOHT. Advances in methylation profiling and computational methods have provided valuable insights into tumor biology. In this study, we performed a comprehensive methylation analysis of SCCOHT samples to delineate the epigenetic landscape of this malignancy. Bioinformatic analyses are utilized such as copy number variation (CNV) analysis and CIBERSORTx to link methylation patterns with established pathological features, further enhancing our understanding of the SCCOHT microenvironment.

Material and Methods: We retrieved a series of 49 SCCOHT malignancies with available tumors tissue from a multi-centre cohort. DNA extraction for methylation profiling was performed on all cases through Genome Quebec using Infinium Methylation EPIC v1.0 and EPIC v2.0 Beadchip assays by Illumina. Unsupervised clustering and t-SNE algorithms were performed using R to highlight the different methylation profile among our cohort. The *conumee2* R package was used to produce copy number variation (CNV) plots and individual CNV profiles were manually inspected. The *methy/CIBERSORT* R package was used to prepare patient methylation data for subsequent analysis in the CIBERSORTx web interface which performs cell-based cytometry analysis of immune cell heterogeneity of each case.

Results: Individual Copy Number Variation (CNV) plots were analyzed visually. Of the 49 cases, 10 displayed high activity of both hyper and hypomethylation across the genome, 34 displayed low activity, and 5 cases displayed intermediate levels of activity. Thus indicating that majority of cases show low levels of hypermethylation and hypomethylation trends.

Conclusions: These findings may offer a new classification framework for SCCOHT and enhance our understanding of the SCCOHT microenvironment and its link to histopathological features. Further research is needed to determine the diagnostic, prognostic, and therapeutic implications of these results.

Source of funding: This work was supported by the Marathon of Hope, Clinician Scientist award.

31 - Role of fibroblast-specific CD109 in the regulation of skin inflammation and fibrosis

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Background: Scleroderma or systemic sclerosis (SSc) is a rare connective tissue disorder characterized by autoimmunity, inflammation and fibrosis of skin and internal organs. SSc fibrosis is driven mainly by transforming growth factor-beta (TGF- β), a potent pro-fibrotic cytokine. We have previously identified CD109, a glycosylphosphatidylinositol (GPI)-anchored protein, as a TGF- β co-receptor that inhibits TGF- β signaling and pro-fibrotic responses in vitro in human skin cells. Furthermore, we have shown that transgenic (TG) mice overexpressing CD109 in the epidermis (keratinocytes) display decreased skin fibrosis in a bleomycin-induced skin fibrosis model and decreased inflammation in lipopolysaccharide (LPS)-induced cutaneous inflammation model, as compared to wild-type (WT) littermates. While the above studies elucidate the role of CD109 expression in epidermal keratinocytes in skin fibrosis and inflammation, the role of CD109 expression in the underlying dermal fibroblasts has not been investigated. The research project is aimed at determining the role of fibroblast-specific CD109 in regulating skin fibrosis and skin inflammation.

Methods: The experimental model will involve a tamoxifen-inducible fibroblast-specific CD109 knockout (KO) mouse model (Col1A2-CreERT2-CD109^{-/-}). The tamoxifen-inducible fibroblast-specific CD109 knockout mice will be generated by crossing CD109 floxed mice with the Col1A2-CreERT2 mice. Affected skin will be harvested and analyzed for immune cell (macrophage, neutrophil and T cell) numbers, pro-inflammatory cytokines (IL-1 α and MCP-1) and NF- κ B signaling pathway components, inflammatory cytokines (IL1- α and TNF- α), and their receptors and downstream transcription factors (p65, c-rel) by immunohistochemistry and qPCR. *In vitro* studies to elucidate the CD109-mediated molecular pathways altered in inflammation and fibrosis will be performed using dermal fibroblasts isolated from the KO versus control mice. Cell lysates and total RNA will be prepared and analyzed for the markers mentioned above by Western blot or qPCR, respectively.

Results: The generation of fibroblast-specific CD109 knockout (KO) mice is currently in progress. My studies are focused on streamlining the methodology using fibroblasts isolated from global CD109 knockout mice and control wild-type (WT) mice. WT and CD109-KO mouse skin fibroblasts were cultured in 12-well plates, but they are struggling to achieve their typical morphology and to adhere properly to the surface. Multiple coats (Collagen coat, Poly-L-Lysine, and Gelatin) and different media conditions (DMEM with high vs low glucose) are being tested to optimize the fibroblast cell culture. So far, the Poly-L-Lysine and Gelatin coatings, in both high and low glucose conditions, appear to be the most effective for the cells.

Conclusions: Skin fibrosis, such as that occurs in scleroderma, is a serious medical problem with limited options for treatment. The proposed research aimed at understanding the mechanism of CD109 action in experimentally-induced skin fibrosis and inflammation will provide mechanistic insight into these disease processes and may lead to a CD109-targeted approach for therapeutic treatment of scleroderma and other fibrotic skin conditions.

Source of Funding: CIHR Project Grant.

32 - Resistive index values of the anterior cerebral artery are associated with the instantaneous levels of cerebral saturation in newborns with congenital heart defects

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Objective: To explore the relationship between near-infrared spectroscopy parameters (Cerebral Saturation [CSat] and corresponding fractional tissue oxygen extraction [FTOE]) and Resistive index (RI) and pulsatility index (PI) of the anterior cerebral artery (ACA) obtained at the same time in neonates with congenital heart defect (CHD) during the first week of life.

Methods: Prospective study on neonates ≥ 35 weeks with CHD. Cerebral FTOE was based on concomitant pre-ductal oxygen saturation (SpO₂) during CSat measurement. ACA was assessed via Doppler ultrasound (US). Continuous CSat/SpO₂ monitoring was collected during the first week of life. Daily ACA-doppler was obtained from day 1 to 7.

Results: 142 concomitant measurements of NIRS and US parameters during the first week of life were collected in 34 neonates with various CHD. Mixed effect models showed significant association between CSat/FTOE and time-corresponding RI-ACA (p 0.02 and 0.005) and PI-ACA (p 0.006 and 0.002), respectively. 0.1-point increase in RI led to 2.3% decrease in CSat and a 3-point increase in FTOE; and 0.1-point increase in PI resulted in a 0.9% decrease in CSat and 1.1-point increase in FTOE.

Conclusion: In neonates with CHD during their first week of life, lower CSat and higher cerebral FTOE were associated with elevated RI and PI values of the ACA obtained simultaneously. Future research should assess whether a multimodal bedside approach to monitoring cerebrovascular hemodynamics can facilitate early detection of cerebral hypoperfusion and prevent brain injury, as well as adverse neurodevelopmental outcomes in this vulnerable population.

33 - Exploring the Relationship Between Physical Activity and Sleep Quality in Pregnant Women with Gestational Diabetes Mellitus

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Background: The interplay between physical activity and sleep quality in pregnant women with gestational diabetes mellitus (GDM) remains an important area of research. Previous studies have shown that women with GDM often experience sleep disturbances, with sleep disordered breathing (SDB) occurring in 17-45% of pregnant women with GDM by the third semester. SDB is associated with a 2-3 fold increased risk of GDM, even after adjusting for obesity. A few studies show a relationship between moderate physical activity and sleep quality in pregnant women, but further exploration between this bidirectional relationship is essential because existing studies on this subject often rely on self-reported data, which can be prone to bias and inaccuracy, whereas objective measurements often provide more reliable data. Exploring this relationship can potentially lead to more effective interventions aimed at improving both sleep and exercise.

The specific questions of this study are:

1. What is the relationship between daily objective assessments of exercise and risk for SDB in the second/third trimester? How does adjustment for BMI affect this relationship?
2. How does physical activity relate to sleep quality (PSQI, objective sleep duration and indices of sleep fragmentation)?
- 3.

Methods: Women diagnosed with GDM were recruited from clinics at 2 academic centers to participate in a randomized control trial (NCT02245659). They wore a SenseWear Armband (SWA) (BodyMedia Inc., Pittsburgh, PA) for one week, providing 24-hour continuous actigraphy and which estimated energy expenditure, intensity of physical activity and sleep-wake activity. Additionally, the patients completed a single-night level 2 screening home polysomnogram to assess sleep patterns and participated in continuous glucose monitoring (CGM) for 72 hours using the iPro2 device.

Results: A total of 59 women met inclusion criteria with a mean age of 35.5 ± 4.2 years, a BMI of 32.7 ± 7.1 kg/m², and at an average gestational age of 29.7 ± 3.6 weeks. Of these participants, 43 wore the SWA device for 90% of the time or more. Among the 59 women, 18 had an Apnea-Hypopnea Index (AHI) of less than 10, while 41 had an AHI of 10 or greater. Participants averaged 4374.2 ± 1624.4 steps per day and had a mean METS of 1.11 ± 0.14 . The average sleep efficiency was 78.01%, with an average Oxygen Desaturation Index (ODI) of 2.14 ± 4.91 events per hour. Preliminary results revealed a statistically significant moderate negative correlation between the average METS and ODI, with a Pearson's correlation coefficient of -0.3886 [95% CI, $-0.51, -0.03$], $p=0.006944$. This finding indicates that an increase in average METS, which measures the intensity of physical activity, is linked to a reduction in the severity of SDB, as assessed by the ODI. In other words, higher levels of physical activity are associated with fewer oxygen desaturation events during sleep.

Conclusion: Our preliminary analysis indicates an early relationship between SDB, which directly impacts sleep quality, and physical activity levels. The next steps in this project involve investigating how these factors are associated with glucose levels and metabolism in pregnant women with gestational diabetes mellitus (GDM).

34 - The Role of CB2 Pathway Modulation in the Downregulation of CD47 Expression and Cell Death Caused by Cannabinoids in Jurkat Cell Line

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Background: CB2, a G-protein-coupled receptor (GPCR), is mainly expressed in immune cells and various cells in the nervous system such as microglia and astrocytes. CB2 has been found to regulate immune functions. Delta-9 tetrahydrocannabinol (THC) acts as a partial agonist for CB2 and CB1, whereas cannabidiol (CBD) has little or no affinity for CB2 but acts as an inverse agonist for CB1. CD47, a transmembrane glycoprotein, plays a vital role in anti-phagocytosis signaling. Recent studies highlight the immunomodulatory effects of CBD and THC. JWH-133 and SR144528 are widely used as CB2-specific agonist and antagonist, respectively. Our study examines the effect of blocking the CB2 pathway on cells treated with CBD and THC in terms of CD47 expression and cell death in Jurkat cell line.

Methods: Studies were performed in vitro; Jurkat cells were cultured and treated with THC (5 μ M) and/or CBD (5 μ M) with and without SR144528 (1, 2.5, 5, 10 μ M) and JWH-133 (5 μ M), and compared with their respective vehicle controls for the expression of CD47 and cell death. Cells were stained for CD47 and zombie dye for live/dead discrimination, and analyzed by multicolor flow cytometry. Flow cytometry data were analyzed using FlowJo software, followed by student's t-tests using Prism.

Results: The expression of CD47 was downregulated in Jurkat cells treated with both the cannabinoids compared to the methanol vehicle (control). The percentage of alive cells also decreased post CBD/THC treatments. Upon the addition of SR144528 at concentrations higher than 2.5 μ M to THC-treated cells, the level of CD47 and the percentage of live cells returned to the baseline. Interestingly, with the addition of SR144528 CB2 antagonist at concentrations higher than 5 μ M to CBD-treated cells, the level of CD47 and the percentage of live cells also increased significantly towards baseline, though not completely. The CB2 agonist did not cause noticeable differences in CD47 expression or the percentage of live cells in either CBD or THC-treated cells.

Conclusion: The downregulation of CD47 and the decrease in live cell numbers caused by THC treatment in Jurkat cells is completely rescued by the CB2-specific antagonist SR144528. Unexpectedly, for CBD-treated cells, there is still a partial rescue at higher concentrations of SR144528. This suggests that although the literature indicates no direct binding between the CB2 receptor and CBD, CBD may cause the downregulation of CD47 and cell death by indirectly increasing endocannabinoid levels in the cells. Alternatively, at higher concentrations, SR144528 may exert off-the-target effects and increase cell viability by undetermined mechanisms.

35 - RAI1 modulates dominance behaviour in mice by regulating interneuron signaling

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Background: RAI1 is a transcription factor that regulates the expression of many genes involved in circuit assembly, neurotransmission, synaptic plasticity, and circadian rhythm in the mammalian brain. Loss of RAI1 function is strongly implicated in the pathophysiology of autism spectrum disorder (ASD), namely a syndromic ASD called Smith-Magenis Syndrome (SMS). In our work, we study models of SMS to understand the neurobiology of ASD because SMS is a single-gene disorder that recapitulates some of the core ASD traits. Although we have established that loss of RAI1 from pan-inhibitory neurons leads to a 'less dominant' mouse compared to its wild-type counterpart, we do not know which specific subtypes of interneurons are involved. The purpose of this project is to identify the role of RAI1 in different subtypes in regulating dominance behavior in both male and female mice.

Materials and Methods: We use mouse genetics to study preclinical models of SMS. We use the Cre/Lox system to conditionally knockout (cKO) RAI1 from vasoactive intestinal peptide (VIP), somatostatin (SST) and parvalbumin (PV) interneurons; all of which are known to modulate dominance behavior in mice. The cKO animals were generated and cryosectioning and immunofluorescence staining was performed to confirm the deletion of RAI1 from VIP, SST and PV cells. The same genotypes were group-housed and trained to cross a small, translucent tube for two days. Once trained, control and cKO animals competed in the 'tube test', in which two animals were allowed to meet in the center of the tube. Whichever mouse retreated from the center within 2 minutes was assigned as the 'loser' and was considered to be submissive to its competitor.

Results: VIP, SST and PV cells showed a 60% reduction of RAI1 in the cKO animals. Results from the tube test showed that deleting one or both copies of RAI1 from VIP cells led to a 'dominance' phenotype whereas loss of RAI1 from SST or PV cells led to a 'submissive' phenotype.

Conclusions: With the research plan outlined, we expect to see that RAI1's role in interneuron functionality is cell-type and context dependent, and it modulates neuronal circuitry regulating social dominance in select brain regions. Overall, this project is the first crucial step towards understanding the role of RAI1 in maintaining INs subtype functionality, and how it is impaired in SMS. Identifying whether loss of RAI1 leads to distinct hypo- or hyperfunction will allow us to develop therapies in order to correct an imbalance in excitation/inhibition to rescue the behavioral abnormalities in ASDs.

Source of Funding: RI-MUHC

36 - Effects of Standard Chemotherapy on Patients with Common Gastric Adenocarcinoma-Related Mutations

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Introduction: Despite advances in treatment, individual differences, such as mutations, limit the effectiveness of chemotherapies. The specific roles of these mutations in drug response remain poorly understood. This study aims to explore the correlation between the response of patients with gastric adenocarcinoma using at least one of the most common drugs used in standard care therapeutics (Fluorouracil and Cisplatin, but not Docetaxel due to its limited use in the present cohort) and the 10 most common gene mutations in these patients (TTN, TP53, MUC16, LRP1B, SYNE1, ARID1A, CSMD3, FLG, FAT4, and CSDM1). Through this project, we intend to set up a protocol of analyzing data of limited scope to test just a couple of factors that influence drug response as a proof of concept. Once a self-consistent analysis system is established, we aim to extend its functionalities and apply to larger cohorts and test a larger set of factors.

Methods: This retrospective cohort study used data from The Cancer Genome Atlas (TCGA) accessed through cBioPortal. The data were filtered and organized manually using Excel. We only included patients with gastric cancer who received standard chemotherapy regimens (Fluorouracil and Cisplatin) and mapped out the common mutations they had. Patient survival status and survival months were used to assess treatment efficacy. Factors such as age and neoplasm disease stage are also taken into consideration. We divided the patients into three categories according to the number of mutations they have among the 10 most common mutations: low mutations (0-2), medium mutations (3-7), and high mutations (8-10). We obtained results for the high mutations category. We will then count the number of patients that responded well to each drug, when categorized by the number of common mutations that they carry. The enrichment or depletion of good response to a drug for a predefined time interval for a patient of a mutation profile will be tested using Fisher's exact test.

Results: Among the 140 patients, eight had eight or more gene mutations among the 10 most common mutations. Out of these eight patients, six were treated with only Fluorouracil, and four of these six patients survived over 18 months, with a median survival of 35.75 months.

Conclusions: This study shows a possibility that gastric adenocarcinoma patients with more than 8 mutations among the 10 most common gene mutations might have more survival months when treating only with Fluorouracil. These findings harbor the potential for further research with larger sample sizes and more sophisticated analyses to confirm and expand on these findings and we will perform statistical tests such as Fisher's exact test to confirm their significance.

Sources of Funding: Montreal General Hospital Foundation US Department of Defense (DoD)

37 - Elucidating of the Effects of Near-physiological Culture Conditions on the Ligamentogenic Differentiation of Bone Marrow-derived Mesenchymal Stromal Cells

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Intro: Anterior cruciate ligament injuries are common musculoskeletal injuries. These hypovascularized tissues persist in relatively hypoxic environments and have a limited regeneration potential. The predominant therapeutic approach involves ACL reconstruction (ACL-R) using auto/allografts; however, ACL-R suffers high failure rates, thus underscoring the urgent need for innovative alternatives. Optimizing *in vitro* culture and differentiation conditions is imperative to harness the potential of stem cells for ligament bioengineering applications. Knowing that ligament tissues and the articular joint space are characterized by lower oxygen tensions compared to arterial and venous blood, maintaining these hypoxic conditions is vital for preserving optimal tissue physiology *in vitro* and ensuring the successful integration of bioengineered grafts. We hypothesize that culturing human bone marrow mesenchymal stromal cells (hBM-MSCs) under near-physiologic oxygen tensions would prime them and enhance their differentiation into the ligamentogenic lineage, thereby offering a promising avenue for ligament tissue engineering. In this study, we aim to elucidate the mechanisms involved in priming and differentiating hBM-MSCs to the ligamentogenic lineage under near-physiologic culture conditions.

Methodology: hBM-MSCs (RoosterBio) were cultured for 10 days at 37°C in 1g/L glucose DMEM supplemented with 5ng/mL TGF- β , 1ng/mL bFGF, and 50 μ g/ml L-ascorbate under three different oxygen tensions: atmospheric and standard cell culture (20% O₂), intravenous (5% O₂), and intraarticular (2% O₂) oxygen tensions. Cell-seeded culture plates were placed in a standard incubator with 5% CO₂ at 37°C for atmospheric oxygen tension. For intravenous and intraarticular oxygen tensions, hypoxia incubator chambers (StemCell Technologies) were sealed, and flushed with 5% O₂ and 2% O₂ gas premixes respectively and placed inside an incubator at 37°C with media changes every 3 days, after which the chambers were resealed and reflushed. After 10 days, the cells were lysed, and the proteins were extracted, quantified, and analyzed using mass spectrometry. Scaffold 5 was employed for protein identification and quantification. The data sets were post-processed, pathway analyses were conducted using ShinyGo 0.80, and functional annotation was performed using David Bioinformatics' National Institutes of Health software.

Results: Biological process, molecular function, and cellular component analyses reveal an upregulation of pathways of cellular response to hypoxia such as HIF-1 signalling pathway and cellular response to reduced oxygen. In addition, our pathway analyses indicate an increase in the glycolytic activity in the cells as we observed the enrichment of pathways pertaining to monosaccharide metabolism and glucose transport across the cellular membrane. Further analysis will look deeper into pathways related to the ligamentogenic differentiation of hBM-MSCs.

Conclusion: These preliminary results reveal possible mechanisms involved in the *in vitro* priming and ligamentogenic differentiation of hBM-MSCs under near-physiological culture conditions. Understanding these mechanisms is crucial to enhance our tissue engineering approaches and develop optimized implantable bioengineered ligament grafts for ligament repair.

38 - BCG vaccination inhibits bone marrow erythropoiesis via IFN- γ

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Background: *Mycobacterium tuberculosis* (*Mtb*) kills 1.5 million people annually. Anemia is a condition commonly associated with Tuberculosis (TB), with a prevalence of approximately 62% in TB patients. Anemia is defined as a deficiency of hemoglobin, which can result from a depletion of erythroid progenitors in the bone marrow (BM). The Bacillus Calmette-Guerin (BCG) vaccine is a live attenuated strain of *Mycobacterium bovis* that protects against *Mtb* infection. Although BCG has demonstrated great efficacy at preventing miliary and meningeal TB in children, the exact mechanism of protection is still unknown. Our lab has demonstrated that BCG generates an innate memory response (trained immunity), which is epigenetically mediated in HSCs to promote myelopoiesis through type II IFN (IFN- γ). In contrast, we have shown *Mtb* suppresses myelopoiesis through type I IFN signaling, which results in iron metabolism dysregulation. Unpublished data from our lab has further identified a long-lasting reduction of erythropoiesis during *Mtb* infection, while this suppression was transient during BCG vaccination with recovery after day 56 vaccination. Given that BCG induces IFN- γ which can directly modulate erythropoiesis, we hypothesize that the transient reduction in BM erythropoiesis results from increased levels of IFN- γ .

Methods: Transcript levels of IFN- γ were assessed in the bone marrow of C57BL/6 mice at days 7, 28, and 56 post BCG vaccination. To further investigate the antagonistic role of IFN- γ in the BM, we vaccinated IFN- γ R^{-/-} mice and wildtype (WT) controls with BCG or PBS controls and compared the levels of erythroid progenitors (Lin⁻Sca1⁻cKit⁺CD150⁻CD105^{hi}Ter119^{hi} cells) at days 7, 28, and 56 post BCG vaccination using flow cytometry.

Results: We observed that IFN- γ levels in the bone marrow peaked at day 28, while there was a concomitant depletion in the levels of all bone marrow erythroid progenitors. Using the IFN- γ R^{-/-} mouse model, we demonstrated that in the absence of IFN- γ signaling, erythropoiesis was restored at day 28 post BCG vaccination as indicated by an increase in all measurable erythroid progenitors compared to the WT controls.

Conclusion and future directions: Our results indicate that IFN- γ inhibits erythropoiesis in the bone marrow during BCG vaccination. The transient increase of IFN- γ following BCG vaccination may serve as a host strategy to provide protection via induction of myelopoiesis at the expense of erythropoiesis. In the future, we aim to explore the mechanism by which BCG vaccination promotes IFN- γ production by assessing cellular sources and measuring cytokines that have been cited to induce IFN- γ production (e.g. IL-12 and IL-18). Additionally, we will investigate the effect of IFN-I on erythropoiesis in the context of BCG infection by using an IFN- α/β R^{-/-} mouse model. Overall, understanding how BCG vaccination reprograms HSCs in the bone marrow is critical for dissecting the cellular and molecular mechanisms involved in trained immunity.

39 - Evaluation of Artificial Intelligence Chatbots in Addressing Most Searched Queries on Psoriasis

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Background: Large language models (LLM) chatbots have the potential to be valuable tools in clinical practice for patient medical education. This study aimed to assess the information quality and accuracy of four different artificial intelligence (AI) chatbots in answering the most frequently queried questions about psoriasis.

Methods: In this cross-sectional study, Google Trends identified the top 25 queries related to psoriasis from January 1, 2021, to January 1, 2023. The subtypes of psoriasis included were general psoriasis, psoriasis arthritis, scalp psoriasis, guttate psoriasis, plaque psoriasis, erythrodermic psoriasis and genital psoriasis.

The 25 queries were entered into the following four chatbots: ChatGPT version 3.5 (OpenAI), Perplexity (Perplexity.AI), Chatsonic (Writesonic), and Bing AI (Microsoft). Two board-certified dermatologists independently graded the responses using the validated modified DISCERN score and the Likert misinformation scale. Understandability and actionability were assessed by medical students using the Patient Education Materials Assessment Tool (PEMAT). Both dermatologists and medical students were single-blinded.

Results: A total of 100 responses from the four chatbots to the 25 psoriasis-related questions were analyzed. Overall, the information quality was generally good across all chatbots, with a median DISCERN score of 4 (Q1=3, Q3=5). ChatGPT ranked highest (median score 5 [4, 5]), followed by Chatsonic (4 [4, 4]), Perplexity (4 [3, 4]), and Bing AI (3 [3, 4]). The Likert scale revealed varying levels of misinformation, from minimal to significant. The median PEMAT Understandability score was 73%, with Chatsonic scoring the highest (median 80% [73%, 82%]), followed by ChatGPT (75% [67%, 80%]), Bing AI (67% [56%, 78%]), and Perplexity (66% [55%, 73%]). Actionability scores were generally poor, with a median PEMAT Actionability score of 40%. Chatsonic scored highest (60% [20%, 60%]), followed by Bing AI (40% [40%, 60%]), ChatGPT (20% [20%, 40%]), and Perplexity (0% [0%, 20%]).

Conclusions: As most chatbots are trained on data from past years, novel therapeutics are often not covered. However, in general, chatbots provided adequate information with Chatsonic performing the best overall. Some misinformation was found regarding treatment recommendations, alternative and home care therapies, and disease etiology. This highlights the need for continuous updates and improvements in chatbot training data to ensure the accuracy and relevance of medical information provided.

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40 - Mapping the Claudin-3 Interactome During Neural Tube Closure in Chick Embryos

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Neural tube defects represent a critical challenge in child and developmental health, leading to conditions such as spina bifida and anencephaly. Understanding the molecular mechanisms underlying neural tube closure—a pivotal event in early embryogenesis where neural folds fuse to form the spinal cord—is essential for developing preventive and treatment strategies. Previously, the Ryan lab demonstrated that Claudin-3, a tight junction protein, is crucial for proper neural tube closure in chick embryos. However, the exact interaction partners of Claudin-3 during this process remain only partially identified. Our research aims to elucidate the protein interactions of Claudin-3 by using a TurboID::Claudin-3 fusion protein to biotinylate proteins in its immediate vicinity. My project focuses specifically on the development and production of the retroviral vector carrying the fusion protein. This involves cloning the TurboID::Claudin-3 construct into the retroviral backbone, growing the virus particles in chicken fibroblast cells, and delivering the virus through microinjection. Upon successful expression, biotin will be administered to the embryos, enabling the biotinylation of proteins adjacent to Claudin-3. These biotinylated proteins will then be isolated and identified through mass spectrometry. Ultimately, this approach will map the Claudin-3 interactome, shedding light on other key proteins involved in neural tube closure. Future work will concentrate on optimizing in vivo biotinylation conditions to ensure robust and specific protein labeling, fine-tuning the timing of infection, and conducting functional studies to validate the identified interactions.

41 - Evaluating the Effectiveness of Machine Learning Models for Detecting Undiagnosed Atrial Fibrillation in Primary Care using electronic health records: A Systematic Review

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Background: Atrial fibrillation (AFib) significantly impacts patient morbidity and mortality, despite existing screening practices. Machine learning (ML) models offer potential for improved detection of AFib from electronic health records (EHR). However, uncertainties remain regarding the performance of these models compared to standard care, their generalizability and applicability in primary care settings.

Objectives

- **To evaluate the effectiveness** of ML models for detecting undiagnosed AFib in primary care settings using EHR, compared to standard care.
- **To assess the quality and generalizability** of ML models by examining the risk of bias and validation approaches.
- **To examine the clinical relevance** of ML models by evaluating outcomes related to patients, providers, and healthcare systems

Methods: Following PRISMA guidelines, we conducted a comprehensive search across seven databases from inception to May 2023. We included studies involving adults in primary care settings where ML models were applied to EHR for detecting new AFib, compared to standard care. Studies that used only ECG or wearable devices for detection were excluded. Data extraction and appraisal were conducted using the Checklist for Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modelling Studies (CHARMS) and the Recommendations for Reporting Machine Learning Analyses in Clinical Research. Risk of bias was assessed using the Prediction Model Risk of Bias Assessment Tool (PROBAST). Clinical applicability was evaluated using the Minimum Information About Clinical Artificial Intelligence Modelling (MI-CLAIM) checklist. Two independent reviewers screened titles and abstracts, selected relevant full-text records, and extracted data using Covidence®. Disagreements were resolved by a third reviewer.

Results: Out of 4,536 references, 16 studies met the inclusion criteria. Most studies were conducted in North America (n=10) and employed retrospective cohort designs (n=12). Less than half (n=6) underwent external validation. Critical appraisal revealed an uncertain risk of bias in most studies due to insufficient reporting on handling missing data. Most studies did not share their codes. Due to significant heterogeneity in performance measures and outcomes, meta-analysis was not feasible. Discrimination performance varied, with the AUROC ranging from 0.71 to 0.948. Seven ML models outperformed control groups. In models that combined ML methods with other clinical tools, a significant improvement in discrimination was observed compared to ML alone. ML identified novel variables for detecting Afib including time-dynamic factors such as recent heart failure diagnoses, cancer, and MRI/echo-based metrics.

Conclusion: Several ML models demonstrated superior performance compared to standard care, especially when combined with other clinical tools. However, significant challenges remain. Uncertain risk of bias limited external validation, and ambiguity regarding code sharing and missing data hinder ML generalizability in primary care. Future research should focus on standardizing reporting performance metrics, model validation, and calibration to improve adoption and reproducibility in primary care.

Source of funding: The Canadian Institute for Health Research project grant

42 - Copy number variation analysis supports diagnosis in vulvar malignant rhabdoid tumours and endometrial sarcoma for a more tailored clinical management

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Background: Uterine malignancies exhibit diverse morphologies, molecular profiles, and clinical outcomes. While most uterine cancers have a favorable prognosis, certain subsets rapidly progress, metastasize, and require aggressive surgical and adjuvant treatment. Unfortunately, the current diagnostic methods for endometrial malignancies are imperfect and often fail to detect Vulvar Malignant Rhabdoid tumors and Endometrial Sarcoma, two particularly aggressive subtypes.

Material and Methods: We retrieved a series of high-grade endometrial malignancies with available tumors tissue from a multi-centre cohort. The morphology of each case was reviewed centrally. Immunohistochemical tests were performed to confirm the undifferentiated nature of the tumors. DNA extraction for methylation profiling was performed on all cases. We used the Infinium Methylation EPIC v1.0 and EPIC v2.0 Beadchip assay (Illumina). Copy Number Variation (CNV) Analysis was performed to explore differential gene expression and compared to known mutations of similar cancers.

Results: We included 32 cases and the analysis of the copy number variations in our series identified a consistent increase in copy numbers for the ARID1B and loss of SMARCB1 genes, with an unchanged SMARCA4 copy number when compared to control data. Certain samples did not express these changes, with some presenting a more baseline presentation, others showing only ARIDB1 upregulation or only SMARCB1 depletion.

Conclusions: Our study suggests that vulvar rhabdoid neoplasms represents a heterogenous disease with many cases showing a copy number profile more akin to ES. Analysis of additional vulvar rhabdoid neoplasm is needed to clarify the diagnostic and clinical landscape of this challenging group of entities. Our result support that copy number variation analysis is a robust approach to help with the diagnosis of endometrial malignancies.

Source of funding: This work was supported by the Marathon of Hope, Clinician Scientist award.

43 - The Importance of Early Diagnosis of Sebaceous Cell Carcinoma of the Eyelid

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Background: Periocular Sebaceous Cell Carcinoma (SbCC) is a rare and malignant tumor of the sebaceous, oil-producing Meibomian glands. It is the most malignant tumor of the eyelid, with up to 33% leading to systemic disease. Pathological evaluation is critical since SbCC can even mimic benign lesions, such as chalazion. SbCC is more commonly seen on the upper eyelid, due to the high concentration of Meibomian glands in this region. The most important prognostic factor is time (6 months) between the onset and the diagnosis of the lesion. The presence of pagetoid spread is also relevant for prognosis. The aim of this study is to examine a large number of patients with SbCC to determine features of favorable or unfavorable prognosis.

Methods: A retrospective analysis was conducted on 62 patients pathologically diagnosed with SbCC at the MUHC-McGill University Ocular Pathology & Translational Research between 1994 and 2023. Data on age, sex and location were collected when available. The study involved a comparison between clinical suspicion and pathological diagnosis, examining pathological features, and immunohistochemical staining.

Results: Of the 62 cases, the average age was 73 years old and 52% (n=32) were males. A total of 56% (n=35) with the main initial clinical misdiagnoses being 16% (n=10) as unspecified carcinoma, 16% (n=10) as Basal Cell Carcinoma, and 10% (n=6) as chalazion. For location, 69% (n=43) were located on the eyelid, with 20 on the upper eyelid, 19 on the lower eyelid, and 4 unspecified as upper or lower eyelid. In addition, 13% (n=8) were exenterations. Pagetoid spread was observed in 26% (n=16) of cases. The immunohistochemical marker, adipophilin was highly positive in all the 9 cases it was performed in.

Conclusions: SbCC is a great mimicker. This fact reiterates the relevance of the pathological evaluation of all eyelid lesions to ensure proper care and earlier correct diagnosis. The location of the lesions being just as prevalent on the lower eyelid can be explained by the number of unusual SbCC received in our Unit. Immunohistochemistry using adipophilin is an important tool for the final diagnosis. The identification of pagetoid spread is crucial to define prognosis. Early detection and intervention are vital for a better patient outcome and quality of life.

44 - The impact of catecholamines and inotropes on bacterial killing by antibiotics

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Background: In the ICU, managing severe infections often requires antibiotics therapy alongside catecholamines and inotropes for septic and cardiogenic shock. However, it is unclear whether these drugs influence bacterial growth and, consequently, antibiotic efficacy. This study investigates the growth of common bacterial strains when exposed to catecholamines and inotropes both alone and in combination with antibiotics, to determine their impact on antibiotic efficacy. Selected bacterial strains were cultured using concentrations corresponding to clinical plasma levels of catecholamines and inotropes to mimic patient conditions in the ICU.

Methods: We cultured three common bloodstream pathogens at varying concentrations of catecholamines and inotropes. Bacterial density was measured over time to assess the impact on growth. Time-kill assays will be performed using beta-lactam and non-beta-lactam antibiotics with the previously determined optimal concentrations of catecholamines and inotropes. This will allow us to assess the measurable effects of these drugs on bacterial replication and antibiotic efficacy. Additionally, shotgun proteomics will be conducted on selected isolates to characterize changes in protein expression, providing insight into the molecular mechanisms involved.

Results: Initial exposure to epinephrine showed no observable effect on the growth of *Escherichia coli* over time. Further analysis of other catecholamines, inotropes, and pathogens is ongoing.

Conclusions: Our findings suggest that epinephrine exposure does not affect *E. coli* growth, indicating its safe use in ICU patients without compromising bacterial proliferation. However, continued studies are necessary to determine the effect of epinephrine on antibiotic treatment efficacy against *E. coli* infection. Ongoing research will further elucidate the effects of other catecholamines and inotropes on different pathogens and their interactions with antibiotics. Understanding these interactions is crucial for optimizing infection management and potentially improving clinical outcomes in critically ill patients.

45 - Elucidating Mechanisms underlying Heterotopic Ossification in muscles of a mouse model of Polytraumatic Spinal Cord Injury.

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Background: Nearly 90,000 cases of traumatic spinal cord injury (SCI) are reported, predominantly resulting from motor vehicle accidents, falls, violence, and sports-related injuries. Heterotopic ossification (HO) is abnormal bone growth in soft tissues and affects around 30% of patients with SCI. Current treatments for HO are non-specific and limited in therapeutic efficacy and off-target side effects. This study aims to examine proteins linked to spinal cord injuries to elucidate the pathogenic mechanisms of SCI-associated HO.

Methods: Six 10-week-old female C56BL/6 mice were subjected to a spinal cord transection to induce a spinal cord injury (SCI), followed by a musculotendinous injury (MTI) by crushing and transecting the left quadriceps muscle and tendon. The first group of mice was euthanized on the following day (Day 1), and the rest six days post-surgery (Day 6). Proteins were extracted, quantified and analyzed using Mass Spectroscopy. The results of both groups are then compared using Scaffold 5 Proteomics Software for analysis.

Results: The preliminary results from the proteomic analysis indicate that Bone Morphogenic Proteins (BMP) could play a role in the development of HO. More specifically, the protein ubiquitin-specific peptidase 9, an essential protein in the TGF- β /BMP signaling, has a fold change of 3.1 from Day 1 to Day 6. The signaling pathway of the BMP group of proteins suggests that it can stimulate the growth of HO by promoting inflammation in the muscles. Another protein, DEAD box helicase 5, has a fold change of 12 between Day 1 and Day 6. This protein is potentially linked to BMPs and skeletal muscle differentiation and could be associated with HO. Further data analysis is still needed to have a deeper understanding of the exact mechanics by which BMPs affect the growth of HO formations. We also hope to find more conclusive data linking the inflammatory responses of macrophages post-injury to the development of HO.

Conclusions: The preliminary findings show that ubiquitin-specific peptidase 9 protein and DEAD box helicase 5 are upregulated on Day 6 compared to Day 1, which suggests the process of ectopic mineralization is potentially linked to the BMP family of signaling proteins. However, due to the small sample size, there is no conclusive evidence about the mechanism behind the interaction or the theoretical link between HO and pro-inflammatory macrophages as stated in current literature. Although the research is still in its early stages, the impact of the analysis could be pivotal in understanding how HO formations work, which could lead to novel and effective treatment of this common post-trauma debilitating condition.

Source of funding: North American Spine Society (NASS)

46 - Rare Diseases: Assessment of the impact of knowledge translation on patients and their families

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Background: Rare diseases are conditions that affect less than 1 in 2000 people. About 3 million people in Canada are affected by rare diseases. Leukodystrophies (LDs) are a group of genetic diseases that affect the white matter of the central nervous system and that are often of progressive nature. As reported by previous studies, patients and caregivers of patients affected by rare diseases, regardless of their etiology or clinical features, experience similar needs and challenges. Knowledge translation (KT) involves generating up-to-date summaries of current research literature findings to make them more accessible to patients. The aim of this research is to investigate the impact of KT and conference attendance, on patients and parents of children with leukodystrophies using questionnaires, survey information, and qualitative data.

Methods: A set of questionnaires is distributed to parents of patients and, when applicable, to patients, in person and online. The questionnaires include a combination of different measures: social support, depression and anxiety, patient and parent stigma, self-efficacy, and perceived knowledge about the disease. Afterward, participants either attend a family conference held by the United Leukodystrophy Foundation or receive an informative brochure containing general information on leukodystrophies and novel therapies. The same set of questionnaires is then administered.

Preliminary results: A T-test was performed to compare the questionnaires' answers before and after conference attendance or reading the brochure, to assess the impact of these support interventions on patients and their families. The results are statistically non-significant, but for each measure, we note an improvement in the scores of some individual participants.

Conclusions: The statistical non-significance of the results could be justified by the small sample of participants. To improve the quality of these results, we aim to recruit a greater number of participants in our study.

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47 - Sex-Specific Associations of IL6R Variants with Aortic Stenosis

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Background: Aortic stenosis (AS) and coronary artery disease (CAD) are cardiovascular diseases with a huge global burden. AS is characterized by the narrowing of the aortic valve, restricting blood flow to the artery and the rest of the body. CAD is caused by a build up of LDL cholesterol deposits in the coronary artery, which reduces blood supply to the heart muscle. Genetics play a key role in both diseases. The Interleukin-6 receptor (IL6R) has been identified as having an important role in the inflammatory response. IL6R mediates the effects of the interleukin-6 (IL6) cytokine that is key to inflammation during immune responses. IL6R and IL6 single nucleotide polymorphisms (SNPs) have been associated with these cardiovascular diseases. Because some inflammatory responses differ between the sexes, we hypothesized that there could be a sex-specific association between genetic variants and the risk of having AS or CAD.

Methods: Data from 432,646 individuals of European ancestry in the UK Biobank included 4974 AS cases and 42,632 CAD cases. Five IL6R SNPs (rs12083537, rs140604580, rs2228145, rs4845625, rs61812626) and one IL6 SNP (rs1800797) were considered. Generalized linear models (GLM) using PLINK 2.0 assessed SNP-disease associations, adjusting for age and sex. The analysis was then repeated, stratified by sex, adjusting only for age. Associations (odds ratios and p-values) were compared between the sexes.

Results: Our analysis demonstrated a sex-specific effect of IL6R SNPs on AS. For each variant, the association was more significant in women than in men. The rs2228145 and rs4845625 variants were significant at the 0.005 threshold level for women. Men failed to reach significance for any of the five SNPs, despite there being more male cases than female cases. This trend was reversed for CAD. For all SNPs other than rs12083537, the odds ratio was more significant in men than in women. The variants rs2228145 and rs4845625 were significant at the 10^{-5} threshold level for men. For women, none of the SNPs reached this level of significance. The IL6 SNP displayed high levels of significance ($p < 10^{-4}$) in both men and women for AS. The association was much weaker for CAD, with p-values > 0.01 in both men and women. In contrast, the IL6R SNPs were more highly associated with CAD than with AS (p-values < 0.05 for rs2228145 and rs4845625) for both men and women. We confirmed the independence of all pairs of SNPs ($R^2 < 0.5$).

Conclusion: An interaction between sex and genetic variants was observed in AS and CAD. In AS, women displayed the protective effects of certain SNP alleles to a larger extent than men. The opposite was observed in CAD. These effects could allow for novel and more precise risk stratification as well as differential target points for developing therapies and treatments.

48 - Evaluating the Impact of Data Curation on Reproducibility of Extracted 11Hz Intra-Breath Oscillometry Parameters

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Background: Spectral oscillometry is a non-invasive method used to assess lung function in finer detail than conventional pulmonary function tests. The current thinking is that removal of artefacts (glottic closure, coughing, or leaking) prior to analysis is required. Further, the inter-rater reproducibility is unknown. Therefore, this study aims to determine if data curation of pressure and flow signals is necessary to reliably derive Resistance and Reactance at the end of inspiration and expiration (cmH₂O/L/s for both Resistance and Reactance), in addition to Reactance-Volume and Reactance-Flow Loop Areas. We hypothesize that curated data will yield more reproducible parameters than non-curated data.

Methods: 23 patients underwent spectral oscillometry testing in 2014 at Dr. Dandurand's pneumology clinic. Analysis was conducted by an incoming Med-2, M.B., two incoming Med-1s, T.A., G.K., and by a PhD engineer, of 50 years' experience, Z.H., who served as the gold standard. The LabView-Based Custom Oscillometry Software extracts 11Hz frequency data from spectral oscillometry tests in order to derive aforementioned intra-breath oscillometry parameters of interest. Data curation involved inspecting pressure and flow signals and removing the above listed artefacts. Subject biometrics, PFTs, spectral and intra-breath oscillometry parameters are expressed as medians and IQRs. Repeatability between raters and between curated and non-curated data was assessed via Bland-Altman plots, Intra-Class Correlation Coefficient, and Cohen's kappa. Statistical analysis was performed using JASP, and TableOne Python.

Results: The curated data does not consistently demonstrate higher precision in oscillometry parameters compared to the non-curated data. Indeed, all confidence intervals include 0 in the Bland-Altman Biases, and the largest mean difference found was only 0.199. Moreover, Intra-Class Correlation Coefficient point estimates range from 0.887 to 1.000, showing high reliability. Cohen's kappa values are more dispersed, showing mixed levels of agreement between raters and between curated versus non-curated data. They range from 0.178 to 1.000 for end-expiration resistance, 0.173 to 1.000 for end-inspiration resistance, 0.173 to 1.000 for end-expiration reactance, and 0.178 to 1.000 for end-inspiration reactance.

Conclusions: The study demonstrates that while data curation aims to improve the quality of oscillometry parameters, the subjective nature of the process introduces its own variability that can offset potential gains in precision. Furthermore, no significant difference was found between curated and non-curated data as compared to the difference that was found between the curated data of the different raters. Thus, curation may be unnecessary in carefully acquired databases such as ours.

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49- Overlooking knee height asymmetry: Is there functional consequences?

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Case: A 21-year-old female, with a 20 mm Knee Height Asymmetry (KHA) post limb lengthening correction surgery, was assessed using a motion capture system. The study focused on biomechanics during jumps, squats and gait to determine whether KHA leads to functional deficits.

Conclusion: The KHA impacted biomechanics more so during functional activities than during gait. This suggests that using functional tasks to understand the impact of KHA may be more appropriate than gait only. Despite having a KHA of only 20 mm, biomechanical asymmetries between sides were evident, suggesting that larger KHAs may lead to clinically significant functional biomechanical abnormalities.

50 - Association of a novel index of early-life growth conditions with chronic obstructive pulmonary disease outcomes

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Background: Chronic obstructive pulmonary disease (COPD) manifests later in life and represents a leading cause of death worldwide. While smoking-related lung pathologies acquired in adulthood are a long-recognized cause of COPD, emerging evidence suggests that early-life growth conditions may play an equally important role. Recently, a novel index of early-life growth conditions, the difference between measured height and genotype-predicted height (height-GaP), has been associated with adverse growth conditions including prematurity, low birth weight, maternal smoking, poor nutrition and multiple deprivation indices. This study aims to evaluate the association of height-GaP with COPD outcomes.

Methods: Among adult participants with spirometry-defined COPD in the SubPopulations and Intermediate Outcomes Measures in COPD Study (SPIROMICS), we computed height-GaP as the difference between standing height and genotype-predicted height. Proportional hazard models were fit for respiratory mortality and all-cause mortality and were adjusted for age, age², sex, race, genotype-predicted height, cigarette smoking status and pack-years. Secondary analyses additionally adjusted for severity of airflow obstruction and investigated height-GaP associations with dyspnea (Medical Research Council dyspnea rating >1) and functional capacity (six minute walk distance).

Results: Among 1,258 participants with COPD (mean±SD age: 65.4±8.0 years, 42.4% female, mean±SD pack-years: 53.6±28.2, mean±SD FEV₁%, 63.3±23.9%), there were 202 respiratory deaths (516 all-cause deaths) over a median of 7.5 years of follow-up. Larger height-GaP deficit was associated with higher respiratory mortality (adjusted hazard ratio [aHR]: 1.30 [95%CI: 1.12 to 1.50] per 1-SD increment in height-GaP deficit) but not all-cause mortality (aHR: 1.09 [95%CI: 1.00 to 1.19] per 1-SD increment in height-GaP deficit). After adjusting the model for COPD severity, the aHR for respiratory mortality remained statistically significant (p=0.016). Larger height-GaP deficit was also associated with higher dyspnea prevalence (prevalence ratio: 1.13 [95%CI: 1.02 to 1.25] per 1 SD increment in height-GaP deficit) and shorter 6-minute walk distance (mean difference = -16.6 m [95%CI: -23.1 m to -10.0 m] per 1 SD increment in height-GaP deficit).

Conclusions: Among adults with COPD, a simple quantitative index of early-life conditions was associated with higher respiratory mortality independent of smoking history and airflow obstruction severity, in addition to dyspnea and reduced functional capacity. These results suggest that early-life growth conditions may influence COPD manifestations and prognosis later in life.

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51- Overcoming resistance: Survivin inhibitor, YM155, promotes Irinotecan-induced apoptosis in colorectal cancer

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Introduction: Colorectal cancer (CRC) is the second leading cause of cancer deaths in the U.S. and involves mutations in genes like APC, KRAS, BRAF, and TP53. TP53 mutations, found in about 60% of CRC cases, cause resistance to chemotherapy. Survivin, an anti-apoptotic protein, is usually suppressed by p53 but is overexpressed in CRC, worsening prognosis.

This study examines the combination of the survivin inhibitor YM155 with the topoisomerase I inhibitor CPT11 (irinotecan) for CRC treatment. We demonstrate that YM155 and CPT11 work synergistically to induce caspase-dependent apoptosis in CRC cells. *In vitro*, we tested the efficacy and synergy of CPT11 and YM155 on human CRC cell line HCT116 using cytotoxicity assays and combination indexes. We then assessed survivin protein levels and the caspase-dependent apoptotic pathway in cells treated with SN-38 (CPT11 active metabolite) and YM155. *In vivo*, the combination treatment was tested in a SCID beige mouse model, with an immunohistological assessment of survivin expression and apoptosis evaluated in tumor samples. Lastly, the separate efficacies of SN-38 and CuET were evaluated in HCT116 TP53 $-/-$ cells.

Results: *In Vitro*: YM155, SN-38, and their combination inhibited HCT116 cell growth dose-dependently, showing synergy at specific doses. More effective CRC cell clonogenicity inhibition was observed in combination than either drug alone. Western Blot analysis showed SN-38 increased survivin protein in HCT116 cells, while YM155 reduced this effect. Combining YM155 with SN-38 also induced caspase-dependent apoptosis, with increased expression of apoptosis-related proteins.

In Vivo: YM155 and CPT11 effectively inhibited CRC growth and induced apoptosis in an HCT116 xenograft model in SCID beige mice. Both drugs alone and in combination significantly reduced tumor growth and tumor weight without causing major toxicity. TUNEL staining showed increased apoptosis in tumors treated with the drug combination, demonstrating a more effective tumor cell death.

Conclusion: Overall, the combination of SN38 and YM155 showed superior results in effectively inhibiting CRC growth and both *in vitro* and *in vivo*, than each drug on their own. The combination treatment overcame SN-38-induced survivin expression increasing caspase-dependent apoptosis. These findings suggest that combining YM155 with CPT11 is a promising CRC therapy that can be developed as a clinical formulation, especially for patients failing current CRC-approved chemotherapies due to high mutational burden.

Source of funding: The project is funded by CIHR, ENOCH and FRQ.

52 - The effect of arsenic exposure on chick embryo development

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Environmental contaminants have the potential to affect normal embryonic development. Contaminants which can cross the placental barrier are particularly harmful to normal fetal development. These substances, which include metallic elements, can cause defects in embryonic development. Arsenic is a toxic metalloid which can be found in high concentrations in groundwater and in certain foods, as well as being a by-product of certain industrial processes. It is a known carcinogen, as well as a risk factor for cardiovascular disease and diabetes. Inorganic arsenic has been previously shown to decrease embryo size and weight, survival rate and angiogenesis in chick embryos. Arsenic has also been shown to be correlated with neural tube defects in human studies with increased prevalence of genetic mutations and epigenetic changes during embryogenesis.

The aim of this project is to study the effects of exposure to inorganic arsenic and its organic metabolites on embryonic development in the chick. We hypothesize that exposure to increasing concentrations of arsenic during early development will lead to an increased prevalence of defects in chick embryos, such as neural tube defects, improper heart looping, and somite defects. In order to establish this relationship, chick embryos were cultured *ex ovo* using two techniques, namely the Cornish Pasty method and the Agar-Albumen plate method. Embryos are collected between Hamburger-Hamilton (HH) stages HH4-HH8 and exposed to varying concentrations of sodium arsenite or monomethylarsonous acid (MMA^{III}). Following a 24-hour incubation at 37°C, embryos are subjected to morphological analysis, and imaged via brightfield microscopy, to examine effects on neural tube closure, somitogenesis and heart tube looping at stages HH11-HH13. Upon analysis, embryos subjected to high concentrations (200 ppb or 2000 ppb) of sodium arsenite or MMA^{III} display increased levels of heart looping defects, somite defects and neural tube defects, demonstrating the toxicity of this metalloid in chick embryos.

53 - Analyzing maternal biomarkers at birth for women with hypertensive disorders of pregnancy and their use in predicting postpartum blood pressure

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Introduction: Hypertensive disorders of pregnancy (HDP), including gestational hypertension and preeclampsia, occur in up to 10% of pregnancies worldwide. Women with HDP have an elevated risk for future cardiovascular disease and chronic hypertension. These women also have lactation difficulties due to low milk supply. While biomarkers such as soluble fms-like tyrosine kinase (sFlt-1), placental growth factor (PlGF), and particularly their ratio (sFlt-1/PlGF) are known to predict preeclampsia and its antenatal complications, their role in predicting postpartum outcomes remains poorly understood.

Materials and Methods: This is a secondary analysis of the she MATTERS study - a multi-centre, open-label, behavioral randomized control trial (RCT) assessing the impact of a nurse-led breastfeeding self-efficacy enhancing intervention versus usual care on postpartum blood pressure and lactation outcomes. As part of the study protocol, sFlt-1 and PlGF were drawn at baseline (within 24 hours of delivery). Women were then followed until 6 months to assess blood pressure and lactation outcomes. The study includes 176 women in the RCT and 10 women in a passive non-breastfeeding control arm. Among the included participants, 95 had blood taken for biomarkers at baseline. We will examine the distribution of these biomarkers according to HDP subtype, and severity of hypertension in hospital. We will analyze the associations between sFlt-1, PlGF, and sFlt-1/PlGF with postpartum hypertension (average office blood pressure exceeding 135/85 mmHg) and with poor lactation outcomes - both collected at 6 months postpartum.

Results: Each of the biomarkers (sFlt-1, PlGF, and their ratio) was normally distributed. The mean sFlt-1 was 819.47 ± 108.21 pg/mL, and the mean PlGF was 19.17 ± 2.21 pg/mL. The mean of the sFlt-1/PlGF ratio was 48.98 ± 6.79 .

Conclusions: The mean sFlt-1/PlGF ratio is well above 38, which is a value known to predict the onset of preeclampsia in pregnant patients at risk for the disorder. We will assess for mean differences in these biomarkers according to different HDP subtypes, the presence of severe hypertension at baseline, and preterm delivery. The relationship between the biomarkers and postpartum blood pressure at 6 months will also be assessed using log-linear regression, adjusting for intervention status and other imbalances in baseline characteristics.

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