

The Institute's 2025 Summer Student Research Day



Journée de recherche des étudiants d'été de l'Institut 2025

Monday

August 11, 2025

8:15a.m. to 3:45 p.m.

Lundi

11 août 2025

8 h 15 à 15 h 45

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 123 résumés des 8 programmes de recherche de L'Institut – accompagnés de présentations orales et 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'Institut. 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.

Nouveauté cette année : des réseaux du FRQS et des départements des études supérieures de McGill tiendront des kiosques d'information. Nous vous invitons à leur rendre visite pendant l'événement pour en apprendre davantage sur leurs programmes et leurs opportunités.

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 123 abstracts from the 8 Institute research programs - with both oral and poster presentations scheduled 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 Institute. 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.

New this year, participating FRQS networks and McGill Graduate Departments will host information tables. We encourage you to visit them during the event to learn more about their programs and opportunities.

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

The Organizing committee

Emily Bell, Ariel De Roo, Anne Mathiot, Inga Murawski, Lenka Schorova, Fanny Toussaint

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 9-16)
- 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 Comparing Motor and Visual Cortex Layer-6 Microcircuits with 2-Photon Optomapping**
Presented by Lareina Shen (Dr. Per Jesper Sjöström – BRaIN)
- 2 A systematic review on the association between pre-term and low birthweight with school readiness in children**
Presented by Maria Jimjees (Dr. Ugochinyere Vivian Ukah – CHHD)
- 3 Regulation of Iron Metabolism and Mitochondrial Health in Diabetic Cardiomyopathy: Therapeutic Potential of Chinese Herbal Medicine**
Presented by Yiting Tang (Dr. Liu Jun-Li – MeDiC)
- 4 Comparative genomics of carbapenemase-producing *Enterobacterales* strains for healthcare-associated infections**
Presented by Elise Wasmer (Dr. Dao Nguyen – RESP)
- 5 Validation and evaluation of Patient Decision Aids (PDA) for Women with Overactive Bladder (OAB) and Stress Urinary Incontinence (SUI)**
Presented by Zoé Frayret (Dr. Maryse Larouche – SIS)
- 6 Characterization and Screening of Antimicrobial Candidates Against *Mycobacterium abscessus***
Presented by Zeineb Haouari (Dr. Andréanne Lupien – IDIGH)
- 7 Lipid Metabolism as a Therapeutic Target in Esophageal Adenocarcinoma: An Exploratory Study**
Presented by Joseph Wang (Dr. Lorenzo Ferri – CRP)
- 8 Long-Term Multisystem Organ Damage Following Pregnancy-induced hypertension: Evaluating the Modifying Effect of Hypertension**
Presented by Mina Hmimas (Dr. Louise Pilote – CHAL)

Session 2 - 12:45-14:20

- 9 Changes in Pediatric RSV-Associated Hospitalizations after the COVID-19 Pandemic, 2022-2023, Canada: A Cross-Sectional Study**
Presented by Aariana Lopes (Dr. Jesse Papenburg – IDIGH)
- 10 Integrating ctDNA and Clinical Parameters to Predict Treatment Response in HPV-Positive Head and Neck Cancer Patients**
Presented by Coralie Lefebvre (Dr. Julia Burnier – CRP)
- 11 Mitochondrial Dynamics and Cellular Resilience Pathways Mediate Heat Stress Hormesis in *C. elegans***
Presented by Mutian Feng (Dr. Jeremy Van Raamsdonk – MeDiC)
- 12 The performance of a machine learning algorithm for the diagnosis of asthma and COPD using respiratory oscillometry in community practice**
Presented by Massimo Catena (Dr. Ronald J. Dandurand – RESP)
- 13 Curing brain cancer with immune cell 'debris' - Characterization of extracellular vesicles derived from lethally irradiated natural killer cells with cytotoxic activity against glioma stem cells**
Presented by Victoria Yip (Dr. Janusz Rak – CHHD)
- 14 Co-designing culturally responsive KTE products with ethnocultural communities: An awareness campaign and policy brief on dementia care**
Presented by Zaina Alsibai (Dr. Claire Godard-Sebillotte – BRaIN)
- 15 Causal Plasma Proteins for Coronary Artery Disease and Aortic Stenosis**
Presented by Xinyi Guo (Dr. James C. Engert – CHAL)
- 16 The Role of CD109 in the Etiology and Progression of Idiopathic Pulmonary Fibrosis**
Presented by Sogand Roohi (Dr. Anie Philip – SIS)

POSTER PRESENTATIONS

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

MORNING SESSION – GROUPS 1-8

Group 1:

- 1-01 Ensuring Data Privacy Through the Development of a Privacy Agent for the MARVIN Self-Management Chatbot Supporting People Living with HIV**
Presented by Aymane Bouchich (Dr. Bertrand Lebouché - IDIGH)
- 1-02 Achieving Accessibility Through the Development of a French Language Translation Module For MARVIN: an HIV Self-Management Chatbot**
Presented by Raisa Chowdhury (Dr. Bertrand Lebouché – IDIGH)
- 1-03 The Translation of “OI Colour, OI Learn” Colouring Book for Italian Children with Osteogenesis imperfecta (OI)**
Presented by Eva Coluni (Dr. Argerie Tsimicalis – CHHD)
- 1-04 Exploring Community Experts’ Perspectives on the Feasibility of Promoting Foundations of Learning and Development (FOLD) Skills in Preschool-Aged Children**
Presented by Rebecca Froio (Dr. Marilyn N. Ahun – CHHD)
- 1-05 Disparities in neurodevelopmental disorders in children by primary spoken language: A comprehensive literature review**
Presented by Bietiel Goniche (Dr. Ugochinyere Vivian Ukah – CHHD)
- 1-06 Evaluating Toolkits for Inclusion, Diversity, Equity and Accessibility in Clinical Trials: A Scoping Review**
Presented by Mélysiane Marcotte (Dr. Louise Pilote – CHAL)
- 1-07 A Decision-Support Algorithm for Optimizing Perinatal Transfers in Quebec: Integrating Objective Data and Occupancy Metrics**
Presented by Maryam Mozafarinia (Dr. Marc Beltempo – CHHD)

Group 2:

- 2-08 Pectopexy vs Sacrocolpopexy techniques for mesh-augmented pelvic organ prolapse apical suspension**
Presented by Jena Bertagnolli (Dr. Maryse Larouche – SIS)
- 2-09 Trends in Causes of Very Preterm Birth and Their Association with Neonatal Outcomes in Canada, 2018-2023: A Population-Based Cohort Study**
Presented by Tiffany Habelrih (Dr. Marc Beltempo – CHHD)
- 2-10 The Association between Hypertension and Accelerated Brain Aging: The Role of Gender-Related Factors**
Presented by Peter Nickoletopoulos (Dr. Louise Pilote– CHAL)
- 2-11 Association of Air Temperature with Cardiovascular Hospitalizations during Summer Periods in Montreal and the Modification Effects of Socioeconomic Factors**
Presented by Sasha Ramkhelawan (Dr. Louise Pilote – CHAL)
- 2-12 Investigating the Extent of Surround Suppression**
Presented by Michael Silverman (Dr. Alexandre Reynaud – BRaIN)
- 2-13 Estimating population size eligible for lung cancer screening in Nunavik**
Presented by Madeline Yaaka (Dr. Faiz Ahmad Khan – RESP)
- 2-14 Hippocampal Development and Its Relation to Executive Function in Adolescents and Young Adults Born Very Preterm and with Congenital Heart Disease**
Presented by Jihong Lee (Dr. Marie Brossard-Racine – CHHD)

Group 3:

- 3-15 Assessing the Impact of Race on Machine Learning Models Predicting Hospital Admissions from Emergency Department**
Presented by Lucy An (Dr. James Tsui – CRP)
- 3-16 Assessing Approaches to Measuring Interpersonal Physiological Synchrony between Dancers and Individuals with Dementia**
Presented by Jessica Coulson (Dr. Stefanie Blain-Moraes - BRaIN)
- 3-17 Improving Coherence and Support in the AI-based MARVIN chatbot via Dynamic Short-Term Memory**
Presented by Daniela D'Aliesio (Dr. Bertrand Lebouché - IDIGH)
- 3-18 Euthyroid Pretibial Mucinous Dermatoses: A Systematic Review of Current Evidence and the Controversy Surrounding Their Classification**
Presented by Raquel Lazarowitz (Dr. Ivan V. Litvinov - CRP)
- 3-19 Efficacy of Upadacitinib for the Treatment of Alopecia Areata: A Systematic Review and Meta-Analysis**
Presented by Raquel Lazarowitz (Dr. Ivan V. Litvinov - CRP)
- 3-20 Development of a Pipeline for CHAMP, a Chatbot to Support Clinical Decision-Making in Pediatric Care**
Presented by Kofi Osel (Dr. Esli Osmanliu - IDIGH)
- 3-21 Occurrence of Intermittent Hypoxemia and Bradycardia in Neonates Prior to Discharge from the Neonatal Intensive Care Unit**
Presented by Sarah Wu (Dr. Wissam Shalish – CHHD)

Group 4:

- 4-22 Baseline circulating tumor DNA as a predictor of clinicopathological features in colorectal cancer**
Presented by Dylan Wu (Dr. Julia Bernier - CRP)
- 4-23 Histopathologic Insights into Good's Syndrome: Persistence of antibody producers in the absence of B cells**
Presented by Dornaz Almasizadeh (Dr. Christos M. Tsoukas – IDIGH)
- 4-24 Evaluation and Optimization of Cold-Spray Copper Powder Coatings for Antibacterial Efficacy Against Nosocomial Pathogens**
Presented by Aarusi Chhabra (Dr. Dao Nguyen - RESP)
- 4-25 The effects of glial glutamate uptake and lipid metabolism on sleep regulation**
Presented by Claire Han (Dr. Donald van Meyel - BRaIN)
- 4-26 Investigating the role of mucolas IgA responses in sex-based differences in bladder tumour development**
Presented by Yasmine Ilkhani (Dr. Éva Michaud - CRP)
- 4-27 Mapping Stress-Induced Activation in the Cerebellum**
Presented by Mona Najafi (Dr. Aparna Suvrathan - BRaIN)

Group 5:

5-28 Promotion of Safe Activities for Children with Osteogenesis Imperfecta

Presented by Evelyn Huaman (Dr. Argerie Tsimicalis - SIS)

5-29 *Second Abstract TBC*

Presented by Evelyn Huaman (Dr. Argerie Tsimicalis - SIS)

5-30 Quality of Life and Stress in Families Affected by a Leukodystrophy: A Longitudinal Study

Presented by Anne Michele Laperrière (Dr. Geneviève Bernard – CHHD)

5-31 Mapping the infrastructure and functionality of the Mental Health Authority's helpline to support individuals experiencing mental health crises in Ghana

Presented by Devena Mahabir (Dr. Marilyn N. Ahun - CHHD)

5-32 The utility of interferon-gamma release assays in the context of a positive tuberculin skin test: a systematic review and meta-analysis

Presented by Raphaëlle Noseworthy (Dr. Jonathon Campbell & Dr. Dick Menzies – RESP)

5-34 Evaluating the impact of a knowledge translation tool for families affected by a leukodystrophy

Presented by Emily Derome (Dr. Geneviève Bernard – CHHD)

Group 6:

6-35 Low-Penetrance CEL-VNTR Frameshifts: A Potential Hidden Cause of Non-Autoimmune Diabetes

Presented by Clara Farhat (Dr. Constantin Polychronakos – CHHD)

6-36 Study of Inflammatory Markers in Ugandan Neonates with Hypoxic-Ischemic Encephalopathy treated with Sildenafil

Presented by Oriane Gimine (Dr. Pia Wintermark - CHHD)

6-37 Analysis of gene variations in the Longitudinal Natural History Study of Patients with Peroxisome Biogenesis Disorders

Presented by Emilie Gros-Slovinska (Dr. Nancy Braverman - CHHD)

6-38 Low-penetrance dominant diabetes due to ABCC8 variants in antibody-negative patients diagnosed with type 1 diabetes (T1D)

Presented by Aiden Shlien (Dr. Constantin Polychronakos – CHHD)

6-39 Maintaining The Phenotype of Primary Human Ligament Cells Using Physiological Oxygen Tensions for Tissue Engineering Applications

Presented by Amir Hossein Taebi (Dr. Rahul Gawri - SIS)

6-40 Sex-Specific Causal Effects of Plasma Proteins on Aortic Stenosis: A Mendelian Randomization Study

Presented by Jeng-Chian Wu (Dr. James C. Engert – CHAL)

Group 7:

7-41 Machine Learning Models for Luminance and Contrast-Defined Boundaries

Presented by Erika Wu (Dr. Curtis Baker - BRaIN)

7-42 Optimizing a Protocol for Post-Irradiation Single-Cell Sequencing

Presented by Samy Boutros (Dr. John Kildea - CRP)

7-43 Modeling Synaptic Heterogeneity to Assess the Limits of Classical CV Analysis

Presented by Jialin Ding (Dr. Per Jesper Sjöström – BRaIN)

7-44 Meta-analysis of scRNA-seq and snRNA-seq reveals differences in transcriptomic heterogeneity between hiPSC-CMs and hiPSC-CM derived organoids, when compared to tissue isolated CMs from healthy and cardiomyopathy patients

Presented by Bryan Lung (Dr. Renzo Cecere - SIS)

7-45 Tripod: Trimodal Methylation Detection from Nanopore Data using Deep Learning

Presented by Juyeon Olivia Song (Dr. Jun Ding - RESP)

7-46 Characterizing clinically relevant Cancer-Associated Fibroblast (CAF) subtypes in Gastroesophageal Adenocarcinoma

Presented by Huayi Tang (Dr. Lorenzo Ferri - CRP)

7-47 Open-source 3D Image Analysis in Python for Mitochondrial Network Analysis

Presented by Alain Zhang (Dr. Rahul Gawri – SIS)

Group 8:

8-48 Investigating novel SH2 domain binding phosphotyrosine residues from pathogenic variants of cancer and Mendelian diseases

Presented by Emma Lee (Dr. Dae-Kyum Kim - CRP)

8-49 TO BE ADDED - prostate cancer, signaling, hormone receptors

Presented by Andrea Bou-Nader (Dr. Simone Chevalier - CRP)

8-50 Assessing the Impact of Four Transcription Factors on the Expression of ECI1 protein in Prostate Cancer Cells

Presented by Xing Chen (Dr. Jacques Lapointe - CRP)

8-51 Effects of Caldesmon Regulation on Smooth Muscle Actomyosin Interactions in the In Vitro Motility Assay

Presented by Christie Liu (Dr. Anne-Marie Lauzon - RESP)

8-52 NMDA receptors determine spine density of cortical layer-5 pyramidal cells

Presented by Kalenga Lubembele (Dr. Per Jesper Sjöström – BRaIN)

8-53 Impact of Mineralocorticoid Receptor on the activation of TRPM7-deficient cardiac fibroblasts

Presented by Liam Quigg (Dr. Rhian Touyz - CHAL)

8-54 Modeling the impact of IPEX-associated FOXP3 mutations on Treg ontogeny using artificial thymic organoids

Presented by Lisa Xie (Dr. Ciriaco Piccirillo – IDIGH)

POSTER PRESENTATIONS

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

AFTERNOON SESSION – GROUPS 9-17

Group 9:

9-01 Dual-peptide functionalized alginate hydrogels mimic nucleus

Presented by Khatra Badreldin (Dr. Lisbet Haglund - SIS)

9-02 A Functional Genomics Approach to Identify Regulators of EZHIP Protein Stability in PFA Ependymoma

Presented by Cylia Bourenane (Dr. Sampath Loganathan & Dr. YiQing Lü - CRP)

9-03 ARHGAP19 Function and Localization in Charcot-Marie-Tooth Disease

Presented by Toulaine Erfan (Dr. Nathalie Lamarche-Vane - CRP)

9-04 Mlp60a and Sallimus are required to restrict branching of developing dendritic arbors

Presented by Alex Hanadel (Dr. Donald van Meyel - BRaIN)

9-05 Development of astrocyte tiling in the mouse visual cortex

Presented by Zoe Harrington (Dr. Per Jesper Sjöström – BRaIN)

9-06 Variants Validating a zebrafish model for PCD variant interpretation using a known loss-of-function DNAAF1 variant

Presented by Ekaterina Ogneva (Dr. Thomas Kitzler - CHHD)

9-07 Development of a 3D Mechanical Stretch Device for Ligament Cell Stimulation

Presented by Pragga Datta (Dr. Derek Rosenzweig – SIS)

Group 10:

10-08 Alterations of brain metabolic profiles in young adult NICU survivors and healthy controls

Presented by Riwa Itani (Dr. Marie Brossard-Racine – CHHD)

10-09 Evaluating the Impact of Blue Chart Reorganization on Healthcare Provider and Research Team Satisfaction in Pediatric Hematology-Oncology: A Protocol Study

Presented by Nona Attaran (Dr. Nicole Sidhu – CRP)

10-11 Comparison of Pressure and Bubbling Sound Properties Across Five Simulated Bubble CPAP Devices

Presented by Jasmine Chapdelaine (Dr. Wissam Shalish - CHHD)

10-12 Assessing the Data Quality of the Shriners International Pediatric AMC Registry: A Metric-Based Evaluation

Presented by Noa Bouzaglo (Dr. Noémi Dahan Oriel - CHHD)

10-13 Association of team composition in the delivery room with outcomes of very preterm infants - a prospective cohort study

Presented by Ava Hodaie (Dr. Marc Beltempo - CHHD)

10-14 The associations between child diet and parental stimulation on early childhood development in Ghana

Presented by Louise Wang (Dr. Marilyn Ahun - CHHD)

Group 11:

- 11-15 Development of an in vitro urothelial model to investigate reverse transcytosis of IgA associated with bladder cancer and sex-specific differences**
Presented by Sirine Bouabda (Dr. Eva Michaud - CRP)
- 11-16 Distinct Commensal Gut Bacteria Induce a Type 1 CD8+ T Cell Response**
Presented by Katja Gollas (Dr. Irah King - RESP)
- 11-18 Bioengineering 3D Intestinal Co-Culture Model as a Therapeutic Screening Platform for Inflammatory Bowel Disease**
Presented by Seong Yeon Kim (Dr. Derek Rosenzweig - SIS)
- 11-19 AtroInC-1 as a Key Modulator of NFkB Signaling in Muscle Autophagy and Inflammatory Responses**
Presented by Geon Park (Dr. Sabah Hussain - RESP)
- 11-20 Exploring Odd-skipped related 1 (Osr1) as a tumour suppressor in bladder cancer**
Presented by Leane Rivard (Dr. Indra Gupta - CHHD)

Group 12:

- 12-21 Characterization of the Dental Abnormalities in POLR3-related Leukodystrophy**
Presented by Paolo Bastone (Dr. Geneviève Bernard - CHHD)
- 12-23 Effect of Hypoxia on Endothelial-to-Mesenchymal Transition in Placental Endothelial Cells**
Presented by Aindrila Kazi (Dr. Mariane Bertagnoli - CHAL)
- 12-24 Benchmarking detection of DNA copy number variation using high-density methylation microarrays**
Presented by Eliza Kishan (Dr. Joanna Przybyl - CRP)
- 12-25 Characterization of Prolactin Induced Phenotypic Changes in Triple-Negative Breast Cancer Patient-Derived Xenografts**
Presented by Angel Soni (Dr. Suhad Ali - CRP)
- 12-26 Characterization of ekl-7 as a potential Enhancer of RNAi**
Presented by Asma Akther Uddin (Dr. Christian E. Rocheleau - MeDiC)

Group 13:

- 13-28 Validity and Acceptability of the Shoebox Tablet-Based Audiometer in School-Aged Children**
Presented by Ninell Sygal (Dr. John J. Manoukian - CHHD)
- 13-29 Comparison of the Bronchodilator Response in Asthma Patients using Respiratory Oscillometry and Spirometry**
Presented by Hana Badawi (Dr. Ronald J. Dandurand - RESP)
- 13-30 Double-blind Crossover Randomized Placebo-Controlled Trial of Modafinil for Fatigue in Mitochondrial Disorders**
Presented by Gabrielle Marquis (Dr. Kenneth Myers - CHHD)
- 13-31 AI-Driven Personalized Exercise Planning for People Living with HIV: An Intervention to Improve Physical Activity and Health Outcomes through the MARVIN Chatbot**
Presented by Krescyn Moonsamy (Dr. Bertrand Lebouché - IDIGH)
- 13-32 Improving Pre-operative Emotional Distress Shortens Hospitalization for Esophagectomy**
Presented by Nisha Suarez (Dr. Trafford Crump - SIS)
- 13-33 Developing a Framework to Evaluate the Impact of Patient Engagement in Esophageal Cancer Research**
Presented by Talia Trottenberg (Dr. Trafford Crump – SIS)
- 13-34 Variability of CA-125 KELIM Scores Across Racial Backgrounds in Patients Undergoing Neoadjuvant Chemotherapy for High-Grade Serous Ovarian Cancer**
Presented by Mira Zaboube (Dr. Reitan Ribeiro – CRP)

Group 14:

- 14-35 Analysis of the PBR and C-terminus domains of CdGAP in the nucleocytoplasmic shuttling of the protein in breast cancer cells**
Presented by Oscar Frohlich (Dr. Nathalie Lamarche-Vane - CRP)
- 14-36 Development and Functional Testing of a Modular CRISPR Base Editing Platform for Hereditary Disease Research**
Presented by Hongxin Li (Dr. Sampath Loganathan & Dr. YiQing Lü - CRP)
- 14-37 RAI1 modulates dominance behaviour in mice by regulating interneuron signaling**
Presented by Sophia Mahiout (Dr. Wei-Hsiang Huang - BRaIN)
- 14-38 Deciphering the Crosstalk between Hippo Pathway Effectors (YAP/TAZ) and E-cadherin in the Progression of Diffuse Gastric Cancer**
Presented by Syed Rayan Rahman (Dr. Alex Gregorieff - CRP)
- 14-39 Senotherapeutics Prevent Disc Degeneration and Back Pain**
Presented by Mavi Sorella (Dr. Lisbet Haglund - SIS)
- 14-40 Investigating the Role of CysLT1 in Nrf2 Activation in Lung Macrophages After Chlorine Inhalation**
Presented by Sadie Wang (Dr. James Martin - RESP)

Group 15:

- 15-41 Validation of Constructs for protein interaction studies**
Presented by Sayma Afroz (Dr. Elena Torban – MeDiC)
- 15-42 Nox5 expression in a vascular smooth muscle cell-specific manner induces fibroblast phenotypic switch and pro-fibrotic effects**
Presented by Eva Brogan-Provencher (Dr. Rhian Touyz - CHAL)
- 15-43 Investigation of protein-protein interactions between CRB2 and EGFR in human podocytes**
Presented by Felix Bui (Dr. Tomoko Takano - MeDiC)
- 15-44 Activation of cardiac fibroblasts observed in TRPM7-deficient cells involves calpain signalling pathway**
Presented by Ella Hamby (Dr. Rhian Touyz - CHAL)
- 15-45 Characterizing the role of IQGAP1 as a novel interactor of Trio in axon outgrowth and guidance**
Presented by Heliya Mirvaghefi (Dr. Nathalie Lamarche-Vane – CRP)
- 15-46 Investigating Herpes Virus U14 Protein as a Modulator of p53 Stability**
Presented by Adèle Usmanov (Dr. Sampath Loganathan & Dr. YiQing Lü - CRP)

Group 16:

- 16-47 Independent Association Between Vitamin D Insufficiency and Liver Fibrosis in People with HIV, regardless of Metabolic Dysfunction-associated Steatotic Liver Disease or Hepatitis C Coinfection**
Presented by Aurgho Datta (Dr. Giada Sebastiani - IDIGH)
- 16-48 Evaluating the Diagnostic Utility of the Kappa Index for Earlier Diagnosis of Multiple Sclerosis**
Presented by Eden Berrebi (Dr. Simon Thebault - BRaIN)
- 16-49 Detection of Acute Kidney Injury in Preeclampsia: A Comparison of Standard Criteria and Kinetic Estimated GFR (keGFR)**
Presented by Maryam Habibagahi (Dr. Stella Daskalopoulou - CHAL)
- 16-50 Clinical Impact of Human Papillomavirus, p53, and p16 Status in Vulvar Cancer: Insights from a Retrospective Single Site Study**
Presented by Taylor Morganstein (Dr. Annie Leung - CRP)
- 16-51 Factors associated with the evolution of HHV8 seropositivity in newly diagnosed people with HIV between 1997 and 2004**
Presented by Natasha Paul (Dr. Jean-Pierre Routy - IDIGH)
- 16-52 Assessing Varicella Zoster Virus Immunity in Immunocompromised Adults on Biologic Therapies**
Presented by Simona Ruscio (Dr. Christine McCusker - RESP)
- 16-53 Trajectories and Determinants of NT-proBNP in the McGill SLE Research Cohort**
Presented by Lucia Zhu (Dr. Sasha Bernatsky – IDIGH)

ABSTRACTS

(alphabetically by last name)

15-41 - Validation of Constructs for protein interaction studies

Sayma Afroz¹, Rita Kalot¹, Elena Torban¹

¹Torban Lab, Department of metabolic disorders, Research Institution of the McGill University Health Center

Background:

Ciliogenesis is a tightly regulated process essential for the formation of primary cilia; cilia serve as critical hubs for signal transduction during development and cell homeostasis. Fuzzy, a planar cell polarity protein, has been shown to regulate cargo trafficking to the ciliary base. Proximity-dependent biotin identification (Bio-ID) revealed that P4HB (prolyl 4-hydroxylase beta) could be a potential Fuzzy interactor. Importantly, mutations in P4HB in humans cause Cole-Carpenter syndrome, a severe skeletal dysplasia, a phenotype often found in diseases with ciliary defects.

Rationale:

To assess potential interactions between Fuzzy and P4HB, we first thought to validate the expression of tagged expression constructs to ensure their suitability for co-immunoprecipitation and other biochemical assays.

Hypothesis and Goal:

We hypothesize that Fuzzy interacts with P4HB. Our goal was to confirm the expression of P4HB-myc-flag, Fuzzy-GFP-flag, and Intu-myc (well-known interactor of Fuzzy) in mammalian cells prior to interaction studies.

Methods:

HEK293T cells were transiently transfected with 1.5 µg of plasmid DNA for each construct using Fugene transfection reagent. After 24-48 hours, 20 µg lysates were collected for western blot analysis. Protein lysates were run on 7% SDS-PAGE gels and probed with anti-myc or anti flag or anti-GFP primary antibodies, followed by appropriate anti-mouse and anti-rabbit secondary antibodies. Protein detection was carried out by ECL assay.

For co-immunoprecipitation, 500-1000 µg of protein lysate was incubated overnight at 4°C with the recommended concentration of anti-myc antibody. Protein G PLUS agarose beads were added for 3 hours, followed by washes with lysis buffer. Bound proteins were eluted in SDS sample buffer and then analyzed by western blotting.

Results:

Visualization under the fluorescence microscope revealed a GFP signal in the cells transfected with Fuzzy-GFP-flag. Western blot analysis demonstrated distinct specific bands for each construct, confirming successful transfection. All proteins were expressed at their expected molecular weights:

- Fuzzy-GFP-flag: ~73 kDa (detected with flag and GFP antibodies),
- P4HB-myc-flag: ~59.2 kDa (detected with both myc and flag antibodies),
- Intu-myc (positive control): ~105.2 kDa (detected with myc antibody).

The bands for P4HB-myc-flag appeared as strong signals on both myc and flag blots, while Fuzzy-GFP-flag and Intu-myc were expressed at moderate levels. Co-immunoprecipitation assays are in progress.

Conclusion:

We validated the expression of P4HB-myc-flag, Fuzzy-GFP-flag and Intu-myc in HEK293T cells. We conclude that these constructs are suitable to investigate the interactions between Fuzzy, P4HB, and Intu. Using Intu-myc as a positive control for Fuzzy interactors will strengthen the interpretation of future binding studies aimed at understanding protein networks in ciliogenesis.

Program MeDiC

PI Dr Elena Torban

4-23 - Histopathologic Insights into Good's Syndrome: Persistence of antibody producers in the absence of B cells

Dornaz Almasizadeh^{1,2}, Aunonna Kabir^{2,3}, Louise Gilbert², Christos Tsoukas^{1,2,3,4}

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Background: Good's Syndrome (GS) is a rare adult-onset immunodeficiency characterized by an association of thymoma and hypogammaglobulinemia. Our previous longitudinal studies identified a complete absence of B cells, progressive cytopenias, and persistent, high-titer anti-cytokine antibodies in GS patients. However, the etiology of this syndrome remains unknown, as is the source of anti-cytokine antibodies when peripheral B cells were undetectable. While peripheral blood immune defects in GS have been described, few studies have examined the architecture and cellular composition of lymphoid tissues. Histopathological analysis can provide critical insight into the nature and extent of immune dysregulation in this syndrome. This study aimed to characterize the lymphoid architecture and cellular composition of primary and secondary lymphoid tissue in GS.

Methods: Original biopsy specimens from our previously characterized GS patients were preserved in formalin-fixed, paraffin-embedded (FFPE) tissue. Samples included an upper paratracheal lymph node from one GS patient, a bone marrow biopsy from another, alongside healthy control tissues obtained from the MUHC Pathology department. Tissue blocks were sectioned and analyzed via immunohistochemistry (IHC). CD3, CD20, and PAX5 were visualized with HRP-Red chromogen (Roche), and CD138 was detected using DAB (brown) chromogen. Hematoxylin was used for nuclear counterstaining. Histological slides were examined using a Leica brightfield microscope at 40× magnification, followed by digital images captured at 10× magnification. Quantification of positively stained immune cells was performed using QuPath image analysis software.

Results: Immunohistochemical analysis revealed a near-complete absence of B cell markers (CD20 and PAX5) in both GS patient tissues. In the lymph node, follicular structures lacked B cells and were predominantly composed of CD3+ T cells. In the bone marrow, the absence of PAX5 suggested a profound depletion of B cell progenitors. CD3+ T cells were relatively sparse in the bone marrow compared to the healthy counterpart. However, CD138+ plasma cells were present in both the GS lymph node and bone marrow tissues, but at reduced levels compared to healthy tissue, where plasma cells were concentrated in germinal centers and interfollicular regions.

Conclusions: These findings confirm that the B cell deficiency in GS extends beyond the blood and is reflected in both primary and secondary lymphoid organs. The absence of both mature and immature B cells suggests a defect or depletion early in B cell development. The presence of CD138+ plasma cells, despite the absence of early B cell markers, suggests that B cells were once present and underwent terminal differentiation before their disappearance. This finding implies the prior existence of functional humoral immunity and is consistent with the typically healthy childhood and early adulthood of GS patients. These tissue-resident, long-lived plasma cells may also represent the source of anti-cytokine antibodies in our GS cohort years following the absence of peripheral B cells. Collectively, these findings offer new insights into the tissue-level pathology and adult-onset immune dysregulation associated with GS.

Sources of Funding: This research is supported by the Anna-Maria Laroche Allergy and Clinical Immunology Research Fund, Montreal General Foundation and Fonds de recherche du Québec.

Program IDIGH

PI Dr. Christos M. Tsoukas

14 - Co-designing culturally responsive KTE products with ethnocultural communities: An awareness campaign and policy brief on dementia care

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Background Equity-seeking ethnocultural communities face significant barriers along their dementia care journeys in accessing healthcare services and receiving timely diagnoses. These challenges are further exacerbated by the scarcity of culturally responsive and tailored resources, and prevalent distrust in healthcare systems due to historic and present discriminatory experiences. Our preliminary scan of the literature and rapid engagement with vested parties emphasized that equity-seeking and high-risk communities are not usually engaged with or targeted when designing broad public health interventions or awareness-raising campaigns. Systematic inequities make it crucial to co-design culturally and linguistically adapted Knowledge Translation and Exchange (KTE) initiatives to increase awareness and trust, address cultural stigma, and highlight experiences of resilience in minoritized communities. Through such KTE initiatives, we also aim to reach policymakers by disseminating the findings from our discussions with community members through a policy brief to ensure that policies reflect community needs.

Methods Using a community-based participatory approach, we co-designed two KTE initiatives with three ethnocultural communities in Ontario and Quebec. Community members were engaged from the pre-design stage, independently designing and generating social media video campaigns tailored specifically to their unique needs (e.g., culturally entrenched stigmas, enhancing knowledge of dementia symptomatology, and fostering self-advocacy among the community). Videos were disseminated through social network platforms used by members of their communities. Additionally, through a series of deliberative dialogues, we engaged with members of the Black Anglophone community in Quebec to understand not only their experiences of encountering inequities in the healthcare system but also their experiences of strength and resilience in the face of these inequities. We also connected with the Alzheimer Societies of Montreal and Laval to leverage their communication channels and gain additional perspective on the issues being presented in the deliberative dialogues. Insights from these discussions shaped a policy brief translating community needs regarding the newly released ministerial policy, the Quebec Alzheimer's Plan (QAP), and will be presented to the Quebec Ministry of Health and Social Services.

Results We expect increased dementia awareness and enhanced health-seeking behaviors within the ethnocultural communities served by our partner organizations. Through videos tailored to community needs, we anticipate that community members will have improved confidence in recognizing and differentiating dementia symptoms from symptoms related to natural aging, greater self-advocacy in discussing symptoms with healthcare providers, and reduced stigma. We will survey community organizations to assess the impact of the videos and track video shares, views, and response. Furthermore, the policy brief will offer actionable, community-identified, and prioritized recommendations for policymakers in Quebec. We will observe whether there are any subsequent changes in policy development, funding allocation, or program implementation related to social determinants of health and mitigating inequity in dementia diagnosis and support in the province.

Conclusion By prioritizing community-defined objectives through direct engagement, this project bridges longstanding gaps between the unmet needs of equity-seeking ethnocultural populations and the broader healthcare infrastructure. Such community-centric methodologies yield culturally pertinent dementia-awareness interventions capable of counteracting systematic barriers, fostering improved dementia care outcomes, and shaping equitable health policy implementation trajectories.

Program BRaIN

PI Claire Godard-Sebillotte

10-09 - Evaluating the Impact of Blue Chart Reorganization on Healthcare Provider and Research Team Satisfaction in Pediatric Hematology-Oncology: A Protocol Study

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Background:

Children followed in the Hematology-Oncology Department at the Montreal Children's Hospital (MCH) have comprehensive paper medical charts that accompany their electronic medical record in Oacis. The paper charts are used for both research and non-research patients, commonly referred to as "blue charts" and specifically document treatment plans, therapy delivery maps (or roadmaps), drug administration guidelines, dose modifications for toxicities, supportive care guidelines, , end-of-treatment and follow-up evaluations, amongst other treatment related details. The blue charts for research patients have even further information, including adverse events reporting requirements and protocol specific details that help guide treatment and evaluation planning. Over time, these charts become extensive and difficult to navigate, leading to dissatisfaction among healthcare providers (HCPs) and research teams. In response, a new Standard Operating Procedure (SOP) was developed to standardize and streamline blue chart content and organization, with input from physicians and clinical staff through meetings and surveys.

Objective:

This study aims to assess the impact of the newly implemented blue chart SOP on the satisfaction of HCPs and research staff who use these charts in routine clinical and research activities.

Methods:

The revised SOP provides standardized guidance on the documentation and organization of blue charts for patients enrolled in clinical trials, including the specific contents that should be in the blue chart, along with clearly labeled sections for treatment roadmaps, dose modifications, supportive care guidelines, and follow-up sections from the research protocols. To evaluate the impact of these structural changes, we will administer the **User Satisfaction Evaluation Questionnaire (USEQ)**, adapted to the context of clinical chart use, to healthcare providers and research personnel who contribute to adding documents and utilize the blue charts. The questionnaire will be distributed via email and will assess satisfaction across key domains such as ease of access, clarity of information, integration into clinical/research workflow, and overall usability. Responses will be analyzed quantitatively using descriptive statistics to identify trends in user satisfaction, with optional open-ended questions included for qualitative feedback.

Expected Outcomes:

The results will inform whether the revised chart format improves user satisfaction and supports clinical and research workflows. If successful, the new structure will be expanded to the charts of children not enrolled on a clinical trial and are following standard of care treatments to promote consistency and accessibility across care settings.

Program CRP

PI Nicole Sidhu

15-42 - Nox5 expression in a vascular smooth muscle cell-specific manner induces fibroblast phenotypic switch and pro-fibrotic effects

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Objective: Mice expressing human Nox5 (hNox5) in vascular smooth muscle cells (VSMC) exhibit redox-sensitive vascular dysfunction and cardio-renal fibrosis. Mechanisms underlying pro-fibrotic effects are unclear. Here we assessed whether hNox5 in VSMCs promotes fibroblast phenotypic changes leading to myofibroblast differentiation and pro-fibrotic/inflammatory responses.

Design and Method: Fibroblasts were cultured from wildtype (WT) and mice expressing hNOX5 in VSMC (Nox5+SM22+). Mice (20 weeks old) were infused with Ang II (600 ng/Kg/day) for 28 days and renal fibrosis/inflammation studied. Markers of myofibroblasts, pro-fibrotic and inflammatory phenotypes were assessed by qPCR and immunoblotting. Inflammatory infiltrate was assessed by FACS.

Results and Conclusion: Fibroblasts isolated from Nox5+SM22+ mice exhibited increased mRNA expression of pro-fibrotic markers, such as Col1A1 (2^{-ddCt} : 1.74 ± 0.16 vs. WT 0.67 ± 0.11), Col3A1 (2^{-ddCt} : 1.74 ± 0.18 vs. WT 0.96 ± 0.24) and TIMP3 (2^{-ddCt} : 2.65 ± 0.25 vs. WT 0.38 ± 0.07), $p < 0.05$. Myofibroblast phenotype (SMC) markers mRNA, α SMA (2^{-ddCt} : 1.54 ± 0.05 vs. WT 0.78 ± 0.17) and Myocd (2^{-ddCt} : 1.36 ± 0.17 vs. WT 0.39 ± 0.22) were also increased in fibroblasts from Nox5 mice, $p < 0.05$. In terms of inflammatory phenotype, we observed that mRNA expression of CD36 (2^{-ddCt} : 1.37 ± 0.07 vs. WT 86 ± 0.24), TNF α (2^{-ddCt} : 1.32 ± 0.2 vs. WT 0.71 ± 0.17) and TNFR1 (2^{-ddCt} : 1.26 ± 0.04 vs. WT 1.02 ± 0.10) were increased, while CD68 expression was decreased (2^{-ddCt} : 0.82 ± 0.11 vs. WT 1.36 ± 0.18) in fibroblasts from Nox5+SM22+ mice ($p < 0.05$). In Nox5 mice fibroblasts, key regulators of fibrosis such as ROS production and TGF β protein expression (AU: 1.8 ± 0.05 vs. WT 1.4 ± 0.06), as well as TGF β R2 gene expression (2^{-ddCt} : 2.04 ± 0.17 vs. WT 0.57 ± 0.12), were increased ($p < 0.05$). Kidneys from Ang II-infused Nox5+SM22+ mice exhibited significant perivascular fibrosis and inflammatory cell infiltration compared to WT. Kidney expression of vimentin (AU: 1.01 ± 0.05 vs WT 0.85 ± 0.03) and α SMA (AU: 0.44 ± 0.03 vs WT 0.33 ± 0.01), markers of myofibroblast differentiation, were increased in Nox5 mice ($p < 0.05$). In kidneys from Nox5+SM22+ mice, increased frequencies of macrophage F4/80+ (%: 24 ± 2 vs WT 18 ± 1 , $p < 0.05$) and cytotoxic CD8+ T cells (%XXX) were increased by Ang II. Our findings suggest that Nox5 in VSMCs influences fibroblast phenotypic switching to myofibroblasts that likely influences cardiovascular and renal fibrosis in hypertension.

Program CHAL

PI Dr. Rhian Touyz

13-29 - Comparison of the Bronchodilator Response in Asthma Patients using Respiratory Oscillometry and Spirometry

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Background: Asthma and chronic obstructive pulmonary disease (COPD) are common respiratory conditions that can significantly impair breathing and reduce quality of life. Assessing lung function is essential for diagnosing these diseases, monitoring their progression, and evaluating treatment efficacy. A key metric used to differentiate asthma from COPD is the bronchodilator response (BDR), a test that measures lung function before and after administering a bronchodilator. While both conditions involve airway obstruction, asthma is often marked by reversible obstruction, whereas COPD is less often so. Oscillometry is a non-invasive technique that evaluates lung function during normal tidal breathing. Compared to the widely used spirometry, oscillometry has been shown to be faster, more convenient, and more sensitive as a point-of-care test. However, despite its advantages, oscillometry lacks well-established reference values for certain parameters, particularly for defining a significant BDR. While a preliminary consensus exists, more thorough investigation is still needed. Establishing such reference values would support the broader adoption of oscillometry in community practice. This study aims to define the criteria for a significant oscillometric BDR by comparing pre- and post-bronchodilator spirometry and oscillometry data in individuals with asthma. We hypothesize that oscillometry will be more sensitive than spirometry in detecting bronchodilator responsiveness among asthma patients.

Methods: We conducted a retrospective chart review to identify asthma patients with same-day pre- and post-bronchodilator oscillometry and spirometry studies. Out of over 500 charts reviewed, 42 patients had all required parameters including biometric data (age, sex, weight, height, BMI), spirometry values (FEV₁, FVC, and MMEF 75/25), oscillometry parameters (R5, X5, FDR, Fres, and AX), and the Asthma Control Questionnaire (ACQ). Absolute and relative changes in oscillometry parameters will be compared across all patients and between those with and without a spirometric BDR using appropriate statistical tests, such as the Student's t-test and the Mann-Whitney U test, adjusting for multiple measures. Finally, BDR status using multiple exploratory thresholds will be compared to the ACQ. Statistical analyses will be performed using JASP (jasp-stats.org), and data table generation and visualization using Python (anaconda.com).

Results: No results are available at this time. We anticipate that defining a significant BDR using oscillometry may require a combination of both absolute and relative changes in parameters and potentially involve a group of parameters rather than a single metric. We also expect that some patients will exhibit a BDR on both spirometry and oscillometry, while others may show a response on only one modality, reflecting the fact that these techniques assess different components of lung function.

Conclusion: Establishing a standard for the BDR value via oscillometry will represent a key step toward the broader adoption of oscillometry in community practice, as this value is crucial for distinguishing between COPD and asthma and following patient treatment. Given oscillometry's greater sensitivity and accessibility as compared to spirometry, its wider adoption could enhance respiratory disease management and improve patient outcomes.

Source of funding: This project is supported by the Kevric Summer Research Bursary and the Dandurand Pneumology Clinic.

Program RESP

PI Ronald J. Dandurand

9-01 - Dual-peptide functionalized alginate hydrogels mimic nucleus

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Introduction

Intervertebral disc (IVD) degeneration is a leading contributor to chronic back pain. Chronic back pain is the leading global cause of disability and has the highest healthcare expenditures of any disease. The nucleus pulposus (NP), the central component of the IVD, is particularly vulnerable to degeneration due to its limited regenerative capacity. Degeneration of the NP leads to a loss of proteoglycans, resulting in tissue dehydration, which reduces the disc's ability to resist compressive forces and ultimately leads to mechanical dysfunction. The most common surgical treatment for IVD degeneration is spinal fusion, however it is a very invasive procedure with inconsistent results and is associated with increased long term risk of degenerative changes in adjacent spine segments.

Here, we present a bioinspired hydrogel system designed to mimic the mechanical and biochemical environment of healthy NP tissue. A hydrogel was engineered to replicate the mechanical properties characteristic of healthy, native NP by incorporating fast stress relaxation. In addition, a dual-peptide strategy was conjugated to the hydrogel to promote cell migration and attachment while enhancing the cell-matrix interactions. These interactions include the incorporation of an $\alpha 2\beta 1$ integrin-binding peptide, and a syndecan-4-binding peptide derived from chondroadherin (CHAD), a matrix protein found in high-pressure connective tissues. CHAD supports a rounded cell morphology desired for healthy NP. Compared to the integrin peptide alone, dual engagement provided by CHAD offers a synergistic approach to NP regeneration. This platform has potential for advancing cell-based therapies and injectable biomaterial strategies in IVD repair.

Methods

Alginate hydrogel (2% w/v) was functionalized with two peptides to enable dual receptor engagement. An integrin-binding peptide (CQLRGLRRWLEAK) derived from CHAD was conjugated to the 2% alginate hydrogel via a thiol-maleimide reaction. A syndecan-binding peptide (CKFPTKRSKKAGR^H), also derived from CHAD, was simultaneously incorporated in a floating (non-covalently tethered) form to allow interaction with syndecan-4 receptors on the cell surface. RGD integrin peptide is used as a positive control. To evaluate cell attachment, mildly degenerative human NP cells were subjected to 2D and 3D attachment assays on the peptide-functionalized hydrogels. NP cells were subsequently encapsulated in the hydrogels for assessment of gene expression related to NP phenotype maintenance.

Results

NP cells activated by the syndecan-binding peptide exhibited significantly enhanced attachment and spreading compared to integrin-only controls. Inclusion of CHAD-derived peptides, particularly the syndecan-binding CKF sequence, upregulated NP-specific genes such as aggrecan and collagen II. These results suggest that dual receptor engagement via integrins and syndecans creates a favorable environment for supporting NP cell phenotype and function.

Conclusion

Our dual-peptide hydrogel system successfully mimics the mechanical and biochemical cues of healthy NP tissue. By integrating both integrin and syndecan-binding motifs from CHAD-derived peptides, we promote NP cell function and phenotype maintenance. These findings support the potential of this biomaterial platform in advancing injectable therapies for IVD regeneration.

Program SIS

PI Dr. Lisbet Haglund

12-21 - Characterization of the Dental Abnormalities in POLR3-related Leukodystrophy

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Background: RNA polymerase III-related hypomyelinating leukodystrophy (POLR3-HLD) is a rare, genetically determined neurodegenerative disorder that affects the white matter of the central nervous system. This condition arises from pathogenic variants in both copies of genes that encode subunits of RNA polymerase III, including *POLR3A*, *POLR3B*, *POLR1C*, *POLR3K*, and *POLR3D*. Clinically, it is often referred to as 4H leukodystrophy, reflecting its cardinal features: hypomyelination, hypodontia, and hypogonadotropic hypogonadism. Symptom onset commonly begins in early childhood, and the disease typically follows a chronic and increasingly debilitating trajectory. Despite hypodontia (i.e., the congenital absence of one to five teeth, excluding third molars/wisdom teeth) being one of the core features of POLR3-HLD, dental abnormalities remain underexplored in the literature. In-depth characterization of these abnormalities may help improve recognition of this rare disorder and guide clinical management. Furthermore, identifying patterns of dental involvement in POLR3-HLD may also offer insight into other rare diseases where dentition is similarly affected, contributing to more comprehensive and multidisciplinary care approaches. We therefore sought to explore and characterize the dental abnormalities observed in patients with POLR3-HLD.

Methods: We are conducting a retrospective clinical chart review of 187 genetically confirmed local, national, and international patients with POLR3-HLD, using data stored in the MyeliNeuroGene Biobank and electronic medical records. All available medical and dental records, and panoramic x-rays (panorex) are being reviewed by the research team. Patient-specific information, including the presence and timing (deciduous vs. permanent) of hypodontia, oligodontia, delayed dentition, abnormal eruption patterns, tooth shape and position, colour changes, caries susceptibility, and other relevant anomalies are being recorded. We are also recording relevant neurological (e.g., whether patients have delayed development, cerebellar features, dysphagia, movement disorders, etc.) and non-neurological (e.g., endocrine, visual/ocular, craniofacial, and skeletal abnormalities) features to explore possible associations with these dental abnormalities.

Results: Preliminary findings indicate that dental abnormalities in POLR3-HLD are heterogeneous between patients. In addition to hypodontia, we observed frequent reports of delayed eruption, abnormal tooth shape and positioning (e.g., ectopic eruption), microdontia (i.e., teeth that are abnormally small), and enamel discolouration. Both deciduous and permanent dentition were affected, with some cases showing congenital absence and others demonstrating significant delays.

Conclusion: Our findings reinforce the role of dental anomalies as a significant clinical component of POLR3-HLD and underscore the need for early dental screening in these patients. This work contributes to the clinical phenotyping of POLR3-HLD and highlights the importance of integrating dental assessment into the multidisciplinary management of leukodystrophies.

Source of Funding: This study is supported by the Montreal Children's Hospital Foundation (Estate of Daphne Dale Townsend) and the Fondation Les Amis d'Elliot.

Program CHHD

PI Geneviève Bernard

16-48 - Evaluating the Diagnostic Utility of the Kappa Index for Earlier Diagnosis of Multiple Sclerosis

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Background

Multiple sclerosis (MS) is the leading cause of non-traumatic neurological disability in young Canadian adults. Early diagnosis can reduce morbidity through prompt treatment. The detection of CSF- restricted oligoclonal bands (OCBs) is a well-established marker of intrathecal immunoglobulin synthesis, and forms part of MS diagnostic criteria. However, OCB testing is subjective, labor-intensive, and costly, resulting in long diagnostic testing delays. We hypothesized that IgG kappa free light chain (k-FLC) index could serve as a supplementary screening biomarker to better target OCB testing which is quicker, cheaper, and more objective. Our aims were to identify the optimal cutoff as a screening test for MS diagnosis and explore associations between k-FLC index and other demographic, clinical and biomarker measures.

Methods

In a prospective observational design, 153 patients under evaluation for neuroinflammation underwent diagnostic lumbar punctures with tandem blood sampling consented for research. Subsequently ascertained diagnoses included 78 with MS, 29 with other inflammatory neurological disorders (OIND), and 51 with non-inflammatory neurological diagnoses (NIND). Tandem CSF and serum k-FLC concentrations were measured on the ThermoFisher Optilite c701 analyzer. The k-FLC index was calculated as (CSF k-FLC /serum k-FLC)/(CSF albumin /serum albumin). OCBs were measured by isoelectric focusing. Diagnostic k-FLC index cutoffs were defined by logistic regression and ROC analysis with Youden's J statistic, examining sensitivity and specificity trade-offs. Spearman correlations were used to explore demographic, clinical and CSF immunophenotypic correlates of k-FLC index.

Results

ROC analysis demonstrated an AUC of 0.81 ($p < 0.001$) for k-FLC index and MS diagnosis. An intersection cutoff of ~9.98 achieved ~74% sensitivity and specificity (positive likelihood ratio ~2.85). MS patients showed elevated k-FLC index compared to both OIND (Mann-Whitney u test $p=1.68 \times 10^{-5}$) and NIND/NN groups (Mann-Whitney u test $p=4.10 \times 10^{-12}$). Constraining our analysis to the 78 patients with MS, we observed strong positive correlations between k-FLC index and OCB count ($r = 0.80$, $p < 0.001$), IgG index ($r = 0.72$, $p < 0.0001$), and CSF IgG synthesis rate ($r = 0.62$ $p < 0.001$). Additional immunophenotyping measures, such as well CSF antibody-secreting cells (ASCs) as a percentage of antibody secreting B cells ($r = 0.72$, $p < 0.0001$) showed a strong relationship.

Overall, the kappa index demonstrated strong, biologically grounded correlations with OCB testing and cellular measures of intrathecal B-cell activity, reinforcing its validity as an alternative diagnostic biomarker.

Conclusions

k-FLC index is a practical and biologically meaningful measure of intrathecal immunoglobulin synthesis that serves as a supplementary diagnostic biomarker in MS. The high specificity observed in our data supports its use as an initial screening test prior to possible confirmatory formal oligoclonal band testing when positive. This may reduce costs and diagnostic delays.

Source of Funding

Supported by internal departmental resources at the McGill University Health Centre. ThermoFisher Scientific provided in-kind assay reagent support.

Program BRaIN

PI Simon Thebault

2-08 - Pectopexy vs Sacrocolpopexy techniques for mesh-augmented pelvic organ prolapse apical suspension

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Background: Pelvic organ prolapse (POP) is a common benign gynecological disorder where pelvic organs such as the vaginal cuff, uterus, bladder or rectum descend from their normal position and protrude through the vagina. Surgical management of POP involves resuspension of the pelvic organs using either native tissues or mesh repair. The gold standard surgery for vaginal vault prolapse is sacrocolpopexy, which consists of attaching a Y-shaped synthetic mesh to the anterior, apical and posterior aspects of the vagina, then anchoring the tail of the mesh to the anterior longitudinal ligament over the sacrum. Although effective, the procedure has a steep learning curve and can be technically challenging especially in elderly, obese, or anticoagulated patients. Key concerns include presacral dissection risks and complexity of patient positioning. As an alternative, laparoscopic pectopexy - an innovative procedure introduced in 2010 - anchors the vaginal apex to the iliopectineal (Cooper's) ligaments, avoiding the sacrum. Initially designed for obese patients, it is now used for those with adhesions or altered anatomy. Pectopexy advantages include reduced blood loss, shorter operative times, and lower risk of neurovascular injury. Our team has performed this technique since 2022. Studying outcomes in a larger population will enhance understanding of its efficacy and safety and contribute to evolving best practices in POP management.

We are aiming to compare baseline, perioperative and short-term postoperative outcomes of pectopexy vs. sacrocolpopexy techniques for surgical correction of POP. We hypothesized that pectopexy is a safe and effective innovative surgical approach for patients with vaginal or uterine prolapse and that operative, perioperative and postoperative outcomes will be superior using pectopexy as compared to the sacrocolpopexy approach.

Methods: We are completing a retrospective cohort study including all women who underwent 1. Pectopexy vs. 2. Sacrocolpopexy at two community hospitals between 2015-2025. We estimate a total of 100 charts will be reviewed. All surgeries were performed by three fellowship-trained Urogynecologists. Data will be analyzed using quantitative data analysis under supervision of a statistician. Data collection will include baseline, operative, and postoperative variables of interest according to our objectives. Main outcomes will be analyzed appropriately to meet the objectives listed previously, including quantitative data analysis under supervision of statistician (including 1. descriptive statistics, 2. paired T-test or chi-square when applicable, and 3. multivariate analysis to identify confounding factors from a predetermined list).

Anticipated Results: We are currently conducting the chart review and preparing the data for statistical analysis.

Conclusions: The purpose of this study is to understand whether laparoscopic pectopexy is a superior surgical method compared to laparoscopic sacrocolpopexy, the current gold standard. To date, there are few longitudinal retrospective cohort studies comparing the two procedures that thoroughly analyze post-operative complications and subjective measures such as pain and quality of life. By contributing to the body of literature, this study can help clinicians make more informed surgical decisions and ultimately influence the management of POP in Canada.

Source of Funding: Funds provided by St. Mary's Research Centre to Maryse Larouche (Clinician-Scientist award) will cover statistical analysis costs.

Program SIS

PI Maryse Larouche

11-15 - DEVELOPMENT OF AN IN VITRO UROTHELIAL MODEL TO INVESTIGATE REVERSE TRANSCYTOSIS OF IgA ASSOCIATED WITH BLADDER CANCER AND SEX-SPECIFIC DIFFERENCES

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BACKGROUND: Bladder cancer is the ninth most commonly diagnosed cancer worldwide, with an estimated 614 298 new cases and 220 596 deaths reported in 2022 by the World Health Organization. The disease shows a strong male predominance, with a 3 to 4 times higher incidence in men than in women. However, women tend to present with more advanced stage tumors and experience poorer outcomes. Immunoglobulin A (IgA), the dominant antibody at mucosal surfaces, plays a critical role in mucosal immunity. While IgA transcytosis has been studied in intestinal epithelium, its mechanisms in the bladder urothelium remain poorly characterized. The phenomenon of reverse transcytosis, the IgA transport from the apical to the basal side of the urothelium, may contribute to immune activation in the tumor environment. Transcriptomic analysis of the TCGA MIBC cohort revealed that IGHA2 expression is associated with improved disease-free survival in female patients, particularly when combined with high ESR1 expression, suggesting a sex-specific role of IgA2 linked to estrogen signaling. Additionally, the gene expression of IgA2 co-receptors Dectin-1 (CLEC7A gene) and Siglec-5 (SIGLEC5 gene) was significantly increased in tumor tissue compared to normal bladder tissue, indicating that bladder tumor cells may interact with mucosal IgA through specific receptors, altering the local immune response to their advantage. The hypothesis is that IgA secretion is not primarily influenced by chromosomal sex but rather by hormonal factors.

METHODS: The orthotopic muscle-invasive bladder cancer (MIBC) model using N-butyl-N-(4-hydroxybutyl)nitrosamine (BBN) was administered in the drinking water (0.05%) of C57BL/6 wildtype and Four Core Genotype (FCG) mice (n=10-15 per sex). FCG mice were used to dissociate chromosomal and gonadal sex effects to bladder carcinogenesis. Enzyme-linked immunosorbent assays (ELISA) were performed to quantify urinary immunoglobulin A (IgA) levels at defined time points (10;15;20 weeks) starting at early point to carcinogenesis. Models of tumoral and epithelial IgA transport were developed by seeding 4.10⁵ RT4 or HBLAK cells per polycarbonate inserts (Millipore) in six-well tissue culture plates. Cells were allowed to colonize inserts for 7 to 10 days and differentiation was assessed by immunohistochemistry.

RESULTS: We report that XX males IgA levels in urine trend lower compared to wild type (XY) males, but we do not observe such differences between FXY females IgA levels compared to wild type (XX) females. The models of tumoral and urothelial IgA transport of the RT4 and HBLAK cell lines, respectively, are currently being developed alongside preliminary attempts to generate bladder organoid. Both models will subsequently be exposed to androgens and estrogens to investigate the hormonal regulation of IgA reverse transcytosis and receptor expression by immunohistochemistry. These findings highlight the potential for sex-specific IgA functionality and tumor-IgA interactions in bladder cancer.

CONCLUSION: Although IgA reverse transcytosis has already been studied in the gut epithelium, this process is not documented in the bladder urothelium. Our findings are contributing to a growing area of cancer research and will fill a gap within the immunological understanding of bladder cancer.

SOURCE OF FUNDING: Canadian Urological Association - bladder cancer Canada operational grant.

Program CRP

PI Eva Michaud

8-49 - Insights into the immune landscape of lethal prostate cancer

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Rationale: Haut du formulaireProstate cancer (PCa) is one of the most frequently diagnosed malignancies in men worldwide. Since it is classified as a cold tumour as a result of a limited immune response, it poses significant resistance to immunotherapy due to its immunosuppressive tumour microenvironment. To improve immunotherapeutic strategies, it is crucial to investigate the immune contexture associated with the prostate tumour microenvironment.

Methods: Banked fresh frozen prostate tissues from 146 radical prostatectomy (RP) cases, 100 with lethal disease and 46 who remained disease-free for more than 10 years post-RP were processed to identify tumour foci and benign glands, macro-dissect tumour cores of high cellularity (>75%) for RNA and DNA extraction and sequencing at high depth as part of the TFRI-Marathon of Hope project. RNA sequencing data were analyzed through CIBERSORTx identifying 22 cell subtypes of the immune system.

Results: Specific immune signatures were identified in benign and cancer samples. The benign prostate tissues displayed higher levels of cytotoxic CD8+ T cells, naïve B cells and T follicular helper cells, known to promote anti-tumour responses. In contrast, macrophages M2 and M1 were predominant in cancer tissues, in line with their role in favoring immunosuppression. Further analysis of immune cell populations according to patients' tumour characteristics highlighted significant correlations between macrophages M2 and M1 with disease progression: the more advanced the blood PSA levels, tumor Gleason grade, tumor stage, and lymph node status, the stronger the immunosuppression was. Similarly, a comparative analysis of immune signatures in benign tissues located near versus far from tumor foci revealed a correlation: the farther the benign tissue is from the tumour, the more immune surveillance is observed. Lastly, a principal component analysis (PCA) showed no distinct clustering by tumor aggressiveness, suggesting that progression is influenced by specific immune cell populations, particularly macrophages, rather than by a global immune profile.

Conclusion: Macrophages are predominantly found in the environment surrounding prostate cancer foci, while cytotoxic immune cells were more prominent in benign samples of the same prostate. This supports both a pro-tumour environment in malignant areas and a protective role in the benign counterparts. The finding of a relationship between macrophages in tumour areas and patients' clinical features underscores the potential for targeting specific immune cells in prostate cancer and warrant further investigation.

Supported by Health Canada, TFRI, MUHC CEDAR Cancer Foundation, and PROCURE.

Program CRP

PI Simone Chevalier

1-01 - Ensuring Data Privacy Through the Development of a Privacy Agent for the MARVIN Self-Management Chatbot Supporting People Living with HIV

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Background: Recent medical advances have allowed people with HIV to live as long as those without, but psychological burdens remain high. To help address this, the AI-based MARVIN chatbot was developed in 2020 to give patients a safe space to ask questions, access reliable information, and receive mental support without burdening healthcare professionals.

For MARVIN to function effectively, it must process patient messages that often contain sensitive information, creating a critical need for strong data protection. A data breach could cause serious stigma and social harm. To prevent this, we developed a privacy agent module that anonymizes messages, keeping them secure yet clear for MARVIN to interpret accurately.

Methods: The first development phase focused on building the privacy agent to pseudonymize sensitive information in input messages, including names, addresses, email, and phone numbers. Instead of deleting or redacting this data, which could disrupt message clarity and confuse MARVIN, the privacy agent replaces it with realistic pseudonyms.

We used prompt engineering with a LLaMA 3.1 8B instruct model to pseudonymize sensitive data. Input messages, generated with ChatGPT using fake names and addresses, simulated real interactions with MARVIN. These messages were then passed through the module in two steps: first, the model identified names, which were then replaced with pseudonyms generated through a Python library; second, the model identified addresses, which were similarly replaced. These steps were combined into a simple pipeline that enables the privacy agent to handle sensitive information one element at a time. We chose this approach because the relatively small 8B model struggled when given multiple tasks at once, so breaking it into two steps improved accuracy and consistency while keeping messages clear for MARVIN. Finally, email addresses and phone numbers were identified and replaced using regular expressions, as their predictable structure (i.e., the “@” symbol) made them easier to handle without involving the model.

Results: Initial testing on 100 ChatGPT-generated input messages, each containing a mix of names, addresses, emails and phone numbers, showed the privacy agent correctly pseudonymized sensitive information about 75 percent of the time. Errors mainly involved the model incorrectly labeling common words such as “daughter” or pronouns like “I” as names, as well as occasionally failing to recognize short first names when they appeared at the beginning of sentences, especially if the names lacked clear context. Despite these issues, the agent preserved message structure and meaning, allowing MARVIN to interpret inputs accurately. The two-pass prompting strategy, which breaks the task into simpler steps, significantly improved performance. Combined with the Python Faker library for realistic pseudonyms, this approach proved efficient and adaptable for handling names and addresses.

Conclusion: These results show that the privacy agent module can protect sensitive patient data without compromising MARVIN's performance. Next steps include refining the model, integrating it into MARVIN, and running tests to ensure continued functionality. Ultimately, this will help secure user privacy while allowing MARVIN to keep supporting people living with HIV.

Source of Funding: This study was supported by RI-MUHC Internal Funding and Polytechnique Montreal.

Program IDIGH

PI Bertrand Lebouché

9-02 - A Functional Genomics Approach to Identify Regulators of EZHIP Protein Stability in PFA Ependymoma

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Posterior fossa ependymoma type A (PFA) is an aggressive pediatric brain tumour driven primarily by epigenetic dysregulation rather than recurrent mutations. A key feature of PFA is the hyperactivity of EZHIP (CXorf67), which mimics the oncogenic histone H3K27M by inhibiting PRC2 activity and reducing H3K27me3 levels. While EZHIP's function in altering the epigenetic landscape is established, the mechanisms controlling its protein stability remain unknown. This represents a critical gap in understanding PFA pathogenesis, as modulating EZHIP stability could offer new therapeutic strategies.

To systematically identify regulators of EZHIP stability, I developed a fluorescence-based reporter system (EZHIP-mClover-P2A-mRFP) in conjunction with the CRISPR-Cas12a gene editing capability, in human medulloblastoma cells, Daoy, which share key epigenetic features with PFA. This reporter enables quantitative tracking of EZHIP protein levels at single-cell resolution. The system was functionally validated, confirming its responsiveness to genetic and chemical perturbations.

Currently, genome-wide CRISPR-Cas12a knockout and activation screens are being performed in the reporter cell line to systematically identify genes that stabilise or destabilise EZHIP. These screens utilise flow cytometry-based sorting to isolate populations with altered EZHIP-mClover levels, followed by sequencing to identify enriched sgRNAs. The findings will provide the first systematic map of genetic regulators controlling EZHIP protein stability in a PFA-relevant context.

As a medical student, this project offers me training in functional genomics, CRISPR screening, and translational neuro-oncology. The results will advance understanding of PFA biology and may reveal novel therapeutic targets for this devastating pediatric cancer. By bridging fundamental discovery with clinical insights, this work exemplifies how functional genomics approaches can address critical gaps in cancer biology and potentially inform future treatment strategies.

Program CRP

PI Dr. Sampath Loganathan, Dr. YiQing Lu

7-42 - Optimizing a Protocol for Post-Irradiation Single-Cell Sequencing

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Background: Our current understanding of ionizing radiation as a carcinogen has improved significantly over recent years. However, our knowledge of how ionizing radiation creates mutations at the DNA level remains incomplete [1]. Current attempts to study these genomic mutations are limited to post-irradiation bulk-cell whole-genome DNA sequencing (piBCS), where irradiated cells are clonally expanded from a single irradiated progenitor cell, sequenced, and their mutations are thus identified. The drawbacks of using this method to indirectly perform post-irradiation single-cell sequencing are its inefficiency and inherent selection effects. To capture the unique radiation damage experienced by each cell, this project aims to study radiation-induced genomic mutations using direct post-irradiation single-cell whole-genome DNA sequencing (piSCS).

Methods: To date, only two groups, including our own which was first, have attempted to use piSCS to observe ionizing radiation-induced mutagenesis. To determine if radiation-induced mutations that were previously identified using indirect piBCS sequencing can be identified using direct piSCS, we will use a novel computer simulation software called RadiSeq that was recently developed by our team. RadiSeq is capable of simulating both indirect piBCS and direct piSCS and is the primary tool for this research project. With RadiSeq, we can cost-effectively optimize a protocol for experimental piSCS by using the radiation-induced mutational signatures observed experimentally by piBCS from Adewoye et al. (2017) [2], Behjati et al. (2016) [3] and from Youk et al. (2024) [4]. We can then characterize and validate the optimized protocol by comparing the experimental results for radiation-induced genomic mutations to our simulated results.

Results: So far, we successfully sequenced and aligned the DNA reads of a small simulation of a radiation-mutated genome of approximately 1500 base pairs. Starting with a small genome allows us to properly assess RadiSeq's performance and modify its behavior while saving both computational time and power. Currently, we are developing a Python script that can take a reference genome of about 100 million base pairs and inject various types of radiation-induced mutations, which we will attempt to detect using both piBCS and piSCS following virtual sequencing using RadiSeq. Finally, we will analyze the coverage of our sequenced mutated genome and determine how well we can detect mutations in the original reference genome. Once these steps are complete, we will be able to compare our simulated results for piBCS to those obtained experimentally and optimize the piSCS portion of our sequencing simulation pipeline.

Conclusion: Our group has already validated RadiSeq's simulation accuracy for detecting DNA damage and copy number variations in comparison with experimental results [5]. However, we are still working to determine whether RadiSeq can reproduce the experimental findings for piBCS and thus accurately detect radiation-induced genetic mutations.

Sources of Funding: NSERC Discovery Grant of Prof. John Kildea.

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Program CRP

PI John Kildea

10-12 - Assessing the Data Quality of the Shriners International Pediatric AMC Registry: A Metric-Based Evaluation

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¹RI-MUHC

Background

Arthrogryposis Multiplex Congenita (AMC) is a rare and heterogeneous congenital condition characterized by multiple joint contractures present at birth, affecting two or more body regions. Due to its complexity and clinical variability, high-quality, standardized data is essential for understanding its phenotypes, etiology, and management strategies. To address this need, the Shriners International Pediatric AMC Registry was launched in 2019, collecting longitudinal data from children with AMC across multiple Shriners Hospitals for Children sites. However, rare disease registries often face challenges in maintaining consistent, high-quality data. This project aimed to evaluate the AMC Registry's data quality using a comprehensive, multi-dimensional framework and to identify opportunities for improvement to enhance its research utility.

Methods

The AMC Registry is a prospective study incorporating retrospective and cross-sectional data across eight Shriners sites, targeting up to 600 participants aged 0-21 years with confirmed AMC diagnoses. Data are managed through a secure REDCap platform and include six distinct forms per patient. Data quality was evaluated using a framework encompassing completeness, duplicity, validity, coherence and comparability, accessibility, usefulness, and timeliness.

Quantitative analysis of extracted REDCap data was conducted using Excel to assess missingness. Review of paper copies of patient forms were conducted to evaluate duplicate questions and to determine the balance of patient-reported vs clinical sources of data. The geographic distribution of recruited patients was analyzed to assess the coherence and comparability of the collected data. Pubmed and thesis searches were conducted to assess the timeliness and usefulness of the registry's contribution to the recent literature. Qualitative assessments, including structured interviews with key personnel, evaluation of established registry protocols and observations of registry functioning, were used to evaluate accessibility and process validity.

Results

The assessment revealed strong foundational integrity of the AMC Registry. Demographic and clinical fields showed high completeness (>95%), while genetic data and functional outcomes had moderate completeness (60-80%), often limited by ongoing follow-up or staffing constraints. Duplicity checks confirmed that most questions were unique, with minor redundancy in the perinatal history section. Validity was supported through standardized CRC training, monthly inter-site meetings, expert case verification, and use of Common Data Elements and Human Phenotype Ontology terms. Comparability and coherence were assessed and demonstrated that approximately half of the data were patient-reported and half were clinician-reported, with multiple sources of secondary data used to support and validate patient-reported information. The assessment also reflected consistent contributions from eight participating sites. A literature review identified 13 peer-reviewed publications and two theses using registry data since launch, with the first paper published within two years. Interviews reflected high satisfaction with the REDCap platform, although challenges included occasional delays in data entry.

Conclusion

The Shriners International Pediatric AMC Registry demonstrates strong data quality and foundational integrity, supporting its value as a reliable multicenter resource for studying a rare and complex condition. Despite challenges in rare disease registries, standardized protocols, multi-site collaboration, and structured data collection have enabled high quality across many metrics. Continued refinement will further strengthen its role in advancing knowledge and care for individuals with AMC.

Program CHHD

PI Dr Noémi Dahan Oliel

15-43 - Investigation of protein-protein interactions between CRB2 and EGFR in human podocytes

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Background. Nephrotic syndrome (NS), an important cause of end-stage kidney disease, is defined by the clinical constellation of massive proteinuria, hypoalbuminemia, edema, and hyperlipidemia, resulting from disruption of the glomerular filtration barrier. While some cases are secondary to systemic diseases, the majority of pediatric and many adult presentations remain idiopathic. Increasing evidence points to an autoimmune etiology underlying idiopathic nephrotic syndrome (INS). Recent work from the Takano Lab has identified Crumbs cell polarity complex component 2 (Crb2), a transmembrane protein localized to the podocyte slit diaphragm, as a potential autoantigen in INS. Immunization of mice with Crb2 induces robust proteinuria, and anti-Crb2 autoantibodies have been detected in a subset of patients with INS, supporting an immune-mediated mechanism. Furthermore, mass spectrometry analysis following proximity biotinylation has identified epidermal growth factor receptor (EGFR) as a candidate Crb2-interacting protein. While Crb2 dysfunction is clearly implicated in proteinuric disease, the signaling pathways by which Crb2 contributes to podocyte injury remain poorly understood. This project aims to characterize the Crb2-EGFR interaction in vitro using HEK293 cells and immortalized human podocytes (HP), to better understand potential downstream signaling mechanisms involved in podocyte dysfunction.

Methods. To establish a Crb2-EGFR interaction, HEK293 cells were transiently transfected with expression constructs for Crb2 and EGFR using Lipofectamine. After 48 hours, cells were lysed, and Crb2 was immunoprecipitated using an anti-Crb2 antibody. Precipitated complexes were separated by SDS-PAGE and analyzed by Western blotting to detect EGFR. The interaction was also tested in reverse by immunoprecipitating EGFR and probing for Crb2. To assess this interaction in a more physiologically relevant system, we utilized a human podocyte line engineered to express Crb2 in a doxycycline (Dox)-inducible manner (HP-Crb2). HP-Crb2 cells were treated with Dox or vehicle, lysed, and subjected to the same co-immunoprecipitation protocol. Finally, to visualize spatial localization, HP-Crb2 cells were fixed and immunostained for Crb2 and EGFR, followed by imaging with confocal microscopy.

Results. In HEK293 cells, EGFR was consistently co-immunoprecipitated with Crb2, confirming a direct or complex-mediated interaction. Reciprocal co-immunoprecipitation also pulled down Crb2 when targeting EGFR, supporting bidirectionality. However, in HP-Crb2 cells, EGFR did not co-immunoprecipitate with Crb2 under the tested conditions, despite successful Crb2 induction. Interestingly, confocal imaging revealed co-localization of Crb2 and EGFR along the plasma membrane, suggesting proximity but not stable complex formation.

Conclusions. Our data support a Crb2-EGFR interaction in overexpression systems like HEK293 cells, but this interaction appears absent or transient in HP-Crb2 cells under basal conditions. This discrepancy may reflect the requirement for a podocyte-specific adaptor protein. Future work will explore whether a podocyte-specific adaptor or signaling context is required for stable Crb2-EGFR complex formation. Given our observation of colocalization in cultured human podocytes, we also plan to quantify Crb2-EGFR colocalization in glomeruli from mouse kidney sections, including Crb2-immunized proteinuric models. These studies may reveal physiologically relevant Crb2-EGFR interactions and their role in the pathogenesis of INS.

Program MeDiC

PI Dr Tomoko Takano

5-31 - Mapping the infrastructure and functionality of the Mental Health Authority's helpline to support individuals experiencing mental health crises in Ghana

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Background: The passage of Ghana's Mental Health Act in 2012 marked a pivotal step toward reforming the country's mental health system. Despite sustained efforts to prioritize mental health through reform and awareness campaigns, Ghana's mental health system remains under-resourced, with poor regional accessibility, workforce shortages and enduring stigma. To address the growing need for mental health advocacy, the Ghana Mental Health Authority (MHA) established a national crisis helpline in 2022 to act as a confidential and accessible outlet for individuals seeking psychosocial support. Though the helpline now extends to all 16 regions of Ghana, little is known about its service delivery, user characteristics and experiences, or how it influences access to care. Therefore, this study seeks to examine the infrastructure, functionality, and user experiences of the MHA helpline.

Methods: This study employed a mixed-methods approach including a qualitative component consisting of semi-structured in-depth interviews (IDIs), and a quantitative component consisting of document reviews that is currently underway. The IDIs consisted of 37 participants, including 17 helpline staff and 20 former callers to capture a range of perspectives on service delivery, caller needs, infrastructure, training, and systemic challenges. The interviews were then transcribed and thematically coded using a collaboratively developed codebook and analyzed through deductive and inductive content analysis.

Results: Preliminary qualitative findings highlight several interrelated domains shaping the operation and perceived impact of the mental health helpline. With regard to **mental health service delivery**, staff described their responsibilities as providing callers with psychological first aid and providing referrals to callers with extensive mental health crises. While many staff shared accounts of successful caller interactions, numerous **infrastructure and resource constraints** were also highlighted. Many helpline staff members emphasized the need for dedicated helpline landlines rather than personal mobile phones, as well as private, sound-controlled environments to ensure caller confidentiality and focus. These limitations were closely tied to **gaps in training**, which staff described as too brief, infrequent, and lacking hands-on practice. Many expressed the need for regular, scenario-based sessions to better support the diverse and complex **needs of callers**. The needs themselves were wide-ranging, with many callers experiencing distress related to financial hardship, interpersonal conflict, or suicidal ideation. A significant number reached out simply because they needed someone to talk to, often citing stigma as the reason they avoided formal care. This speaks to a broader public misunderstanding of the helpline's purpose, with staff highlighting the importance of mental health education and awareness to clarify that the helpline is a space for emotional support rather than material aid, and to reduce stigma so individuals feel empowered to seek help without fear or shame. Results from the quantitative component are currently under analysis.

Conclusions: Ghana's national helpline offers a critical entry point for mental health support, particularly for individuals deterred by stigma or lack of regional access. However, its impact is limited by infrastructure gaps, inconsistent training, and public misconceptions. Therefore, strengthening resources, staff support, and awareness efforts is essential to fully maximize the helpline's potential as a national mental health service.

Program CHHD

PI Marilyn N. Ahun

12 - The performance of a machine learning algorithm for the diagnosis of asthma and COPD using respiratory oscillometry in community practice

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Background: Respiratory oscillometry, a non-invasive lung function test, is emerging as a more sensitive and patient-friendly tool for early detection of lung diseases such as asthma and chronic obstructive pulmonary disease (COPD) compared to spirometry. However, its clinical adoption remains limited due to lack of familiarity and complexity of data interpretation for non-experts such as general practitioners. A recently developed machine learning (ML) algorithm by the University of Toronto shows promise in automating oscillometry analysis, potentially improving accessibility for clinicians in community settings. This project aims to evaluate the performance of this algorithm on real-world oscillometry data and determine its accuracy in distinguishing between asthma, COPD, and healthy individuals.

Specific Aims: To validate the UofT ML in oscillometry data collected in a different patient population of a community respirology clinic.

Study Population and Methods: Oscillometry and standard PFT data from a single community practice (Clinique pneumo Dandurand, Kirkland, Canada) where over 1800 subjects have undergone oscillometry since 2014 will be used. 100 asthma, 100 COPD, and 100 healthy subjects with oscillometry and spirometry conducted within 6 months of each other, were randomly selected for evaluation with the ML algorithm. The ground truth label will be based on physician diagnosis and standard pulmonary function tests. The primary end point will be comparison of the machine learning label to the ground truth label. Statistical analyses will be performed using JASP (jasp-stats.org), and data tables and visualization using Python (anaconda.com).

Expected Results: Based on previous work by our collaborators at the University of Toronto, we expect the machine learning algorithm to accurately distinguish between asthma, COPD, and healthy subjects using oscillometry data (Tisi M, et al., Eur Respir J 2023;62(suppl 67): OA874.). The algorithm demonstrated accuracy in predicting patterns of pulmonary function from oscillometry signals and classifying the signals into four major lung function patterns of obstructive, restrictive, mixed and normal. The algorithm achieved significantly higher accuracies than experts. We anticipate comparable results in our real-world community cohort. If accuracy is not met, a secondary objective will be to send the data to UofT to improve the accuracies of the architecture.

Conclusions: This study potentially establishes a foundation for validation of an automated diagnostic tool for asthma and COPD using real-world community data. Once our analysis is complete, the findings will likely help determine whether machine learning can reliably interpret oscillometry results in non-specialist settings. If successful, this approach could significantly reduce barriers to widespread oscillometry use and improve diagnostic accuracy in primary care.

Program RESP

PI Ronald J. Dandurand

10-11 - Comparison of Pressure and Bubbling Sound Properties Across Five Simulated Bubble CPAP Devices

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Background: Bubble continuous positive airway pressure (CPAP) is an easy-to-use and inexpensive non-invasive respiratory support system commonly used in the neonatal intensive care unit (NICU). Humidified air is delivered to the neonate through nasal prongs and system pressure is set by expiratory limb submersion depth. As air escapes, bubbles form and create oscillatory pressure that is transmitted back to the neonate's airways and lungs, promoting airway patency, lung development, and effective gas exchange. Given that pressure catheters are expensive and impractical for continuous use, NICU staff manually verify the system routinely for leaks or obstructions by listening to the bubbling sounds. Previous manikin studies in a controlled environment have demonstrated that the acoustic properties of the bubbling sounds accurately predict delivered pressures in the standard-of-care bubble CPAP device used at the Montreal Children's Hospital, the Fisher & Paykel. Yet, there are many variations between devices on the market, such as water canister size, submersion angle of the expiratory limb, and tubing diameter, all of which impacts the sounds of bubbles produced and the quality of therapy delivered. Thus, we aim to compare the properties of pressure and bubbling sounds across five different bubble CPAP devices.

Methods: A 36-week term manikin with anatomically accurate upper airways was connected to a bubble CPAP system via a standardized nasal prong interface (Babi.Plus nCPAP kit). In a quiet room, bubbling sounds were recorded with a Lavalier microphone placed on the water canister, while delivered pressure was measured with a pressure catheter in the expiratory tubing of the system. Sound and pressure were recorded for different combinations of pressure (5, 6, 7, 8 cmH₂O) and flow (6, 8, 10 L/min), for a total of 12 trials of 5-minutes each. To ensure replicability, this experiment was repeated three times and conducted using 5 bubble CPAP devices: Fisher & Paykel Bubble CPAP, Seattle PAP Plus Bubble CPAP (Dräger), Vayu Bubble CPAP, the original Bubble BabiPlus by Respirologics and their new premarket Bubble BabiPlus 7.3 device. For each device and across all setting combinations, pressure (mean and standard deviation) and sound (root mean square) metrics were calculated in MATLAB in 30-second segments. Variations in sound metrics were compared between the different devices using one-way ANOVA. Pressure metrics were also compared by the same method. Finally, the relationship between sound and pressure metrics was evaluated using Pearson correlation coefficients and compared across different devices.

Results: Data collection is currently underway.

Conclusions: Data collection will be completed by August 1st, and analysis finalized by August 8th. We anticipate that there will be differences in the pressure-sound relationship of each device, but that the properties of the bubbling sounds will accurately predict delivered pressures in every system.

Funding: This project is generously supported by the Nicholas McCutcheon Research Bursary in Medicine. Dr. Shalish's team, the Smart Hospital Project, is funded by the Montreal Children's Hospital Foundation, the Research Institute at the McGill University Health Center, the Fonds de Recherche Québec Santé, and the McGill Innovation Fund at McGill University.

Program CHHD

PI Dr. Wissam Shalish

8-50 - Assessing the Impact of Four Transcription Factors on the Expression of ECI1 protein in Prostate Cancer Cells

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Background

Prostate cancer (PCa) outcome is highly variable between different patients, creating the need to develop novel prognostic tools and treatment options. Genomic alterations detected in PCa cells, such as a gain at chromosome 16p13.3 locus, could serve as biomarkers to predict poor clinical outcome. The *ECI1* gene, a potential driver of the 16p13.3 gain, codes for the enzyme Δ^3, Δ^2 -Enoyl-CoA Delta Isomerase 1 (ECI1), which degrades fatty acids through β -oxidation to provide energy for cancer growth. ECI1 overexpression is associated with PCa progression and generally linked with the 16p13.3 gain, yet 30% ECI1-overexpressing tumors do not harbour this gain, suggesting that another mechanism stimulates the high production of ECI1 protein. It is crucial to find this cause of ECI1 overexpression because it can potentially be targeted in new treatment methods to decrease the production of ECI1. Four transcription factors (TFs) — ESRRA, MAZ, NR2F6, and ZNF511 — have been identified as potential regulators of ECI1 expression based on bioinformatic analyses. This project aims to assess the impact of each of the four TFs on ECI1 expression in PCa cells. We hypothesize that one or more of these transcription factors play a regulatory role on ECI1 expression, and their activity drives ECI1 overexpression in the absence of a 16p13.3 gain.

Methods

The expression of the four TFs will be each knocked down by siRNAs in C4-2 cells, a prostate cancer cell line expressing high levels of ECI1 but does not harbor a 16p13.3 gain. Western blot analysis and RT-qPCR will be performed to assess the effectiveness of the TF knockdowns and the impact on ECI1 expression.

Results

siRNAs cell transfections were carried out and we are currently assessing the TFs knockdown and its impact on ECI1 expression.

Conclusions

If the hypothesis is correct, the knockdown of at least one TF will significantly reduce ECI1 levels shown on both Western blot and RT-qPCR. The TF that influences ECI1 expression the most can be examined to find other genes under its regulation, which are expected to be involved in fatty acid oxidation along with ECI1. This TF can be served as a new biomarker for prostate cancer prognosis and as a potential therapeutic target to limit ECI1 overexpression.

Source of funding

The source of funding for this project is the summer research bursary program.

Program CRP

PI Jacques Lapointe

4-24 - Evaluation and Optimization of Cold-Spray Copper Powder Coatings for Antibacterial Efficacy Against Nosocomial Pathogens

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Introduction: Healthcare-associated infections (HAIs) remain a major public health concern, particularly in hospital settings where high-touch surfaces (HTSs) serve as persistent reservoirs for opportunistic pathogens like *Pseudomonas aeruginosa* and *Staphylococcus aureus*. Traditional cleaning methods, while effective, are labor-intensive, costly, and lack continuous antimicrobial protection. Copper, known for its natural antimicrobial properties, has re-emerged as a promising material for self-disinfecting surfaces. Recent advances in cold-spray technology allow copper and copper-alloy powders to be applied as durable, uniform coatings on existing infrastructure, providing passive, long-lasting protection. Unlike bulk copper, which is expensive and difficult to scale, cold-gas spray (CGS) accelerates metal powders at high velocity without melting them, forming dense, corrosion-resistant coatings with minimal oxidation. CGS is a cost-effective, scalable approach for developing antimicrobial surfaces in healthcare environments.

Material & Methods: This study assessed the antibacterial efficacy of various copper powders against *Pseudomonas aeruginosa* and *Staphylococcus aureus*, using *P. aeruginosa* as the primary model organism. Standardized bacterial cultures were prepared in tryptic soy broth and adjusted using optical density measurements. A modified EPA time-kill assay was used to test antibacterial activity. Bacterial suspensions containing a simulated organic soil load to mimic real life situations, were applied to a range of test powders, including pure copper, aged powders, oxidized powders, copper alloys, and stainless steel (negative control). This aimed to evaluate how factors like oxidation, aging, and alloy composition influence antimicrobial efficacy. At defined time points, samples were neutralized with Lethen broth, serially diluted, and plated on tryptic soy agar for CFU enumeration.

Results: Copper powders demonstrated strong antimicrobial activity against *Pseudomonas aeruginosa*, with up to 99.99% bacterial reduction observed within 30 minutes. Several formulations achieved complete killing within just 2 minutes, in contrast to stainless steel controls, which showed negligible reduction. The findings highlighted clear differences in performance based on powder characteristics with composition, oxidation level, and production method all influencing antimicrobial efficacy. These results provide key insight for selecting optimal candidates for cold-spray coating, isolating the most intrinsically active copper powders prior to surface application.

Conclusions: This study demonstrates the utility of powder-based screening as an effective strategy to evaluate the inherent antimicrobial activity of copper materials. By identifying key properties that contribute to rapid bacterial killing, this approach lays the groundwork for designing optimized cold-spray copper (CuCS) coatings for real-world applications. Assay optimization is ongoing to improve detection limits and explore high-throughput alternatives to CFU enumeration. Future work will expand testing to additional clinically relevant pathogens, beginning with *Staphylococcus aureus* and progressing to other ESKAPE pathogens, ultimately supporting the development of broad-spectrum antimicrobial coatings to reduce surface-borne transmission in healthcare environments.

Source of Funding: The project is supported by the National Research Council Canada (NRC) and the Natural Sciences and Engineering Research Council of Canada (NSERC).

Program RESP

PI Dao Nguyen

1-02 - Achieving Accessibility Through the Development of a French Language Translation Module For MARVIN: an HIV Self-Management Chatbot

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Background: In Canada, and particularly in Québec, HIV continues to disproportionately affect marginalized communities, including immigrants, racialized populations, and people with limited access to culturally and linguistically appropriate care. Digital health tools, such as mobile health (mHealth) interventions and AI-powered chatbots, have demonstrated promise in supporting people living with HIV (PLWH) by promoting medication adherence, symptom monitoring, and engagement with care. However, in a multilingual context like Québec, language remains a critical barrier to equitable access and engagement with these tools.

To address this need, our team developed MARVIN in 2020, an AI-based self-management chatbot designed to support PLWH. To improve accessibility, this research aims to develop a context-sensitive, culturally appropriate French translation module that enables real-time bilingual interaction within a single server. This work seeks to enhance the inclusivity and efficiency of MARVIN, with the potential to expand its use across additional language groups in the future.

Method: Background research and cost estimates were carried out for a range of translation models to determine the efficiency of each translation process. Google Cloud Translate's Adaptive translation model was selected due to their strong performance in health-related language tasks and support for custom models, which allow for context-specific and culturally sensitive translations.

A custom component using Google Cloud Translate's API calls was then developed using RASA, an open-source machine learning framework, and integrated into the RASA pipeline (the existing MARVIN model). This translation component translates French inputs into English, enabling the English Natural Language Unit (NLU) processing to generate a response. The generated English responses are then translated to French, using a complementary translation module, to send back to the user.

To assess the module's usability, small-scale pilot testing will be conducted at the Research Institute of the McGill University Health Centre with bilingual users, including focus group discussions with existing MARVIN patient partners. The study will explore usability (e.g., ease of use, clarity of conversation) and acceptability (e.g., tone, contextual accuracy, trust in responses, cultural sensitivity). In addition to qualitative feedback, a brief System Usability Scale (SUS) survey will be administered to quantify overall usability.

Expected Results: The translation module of MARVIN is expected to enable users to have contextually appropriate, clear, and engaging conversations in French. Outcomes of interest include high ratings of usability and acceptability, which will inform future refinement of the module, measured by users' perception of tone, trust, contextual alignment, and cultural sensitivity. Feedback from patient partners will be used to improve the module and guide the broader scaling of MARVIN to multilingual contexts.

Conclusion: The development of a context-specific translation module has the potential to significantly enhance the accessibility of mHealth chatbots like MARVIN, particularly for underserved and multilingual populations, while also enabling broader scalability. Future development will include expanding the translation module to detect additional languages, starting with the topmost spoken languages in Montreal, including Arabic, Spanish, Italian, and Mandarin.

Source of Funding: This study was supported by the Unité Soutien SSA and RI-MUHC Internal Funding.

Program IDIGH

PI Dr. Bertrand Lebouche

1-03 - The Translation of “OI Colour, OI Learn” Colouring Book for Italian Children with Osteogenesis imperfecta (OI)

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Background: Osteogenesis imperfecta (OI) is a rare genetic condition primarily affecting the bones, resulting in increased susceptibility to fractures and decreased bone density. Also known as “brittle bone disease,” OI impairs the formation of strong bones and significantly raises the risk of painful fractures and deformities. The “OI Colour, OI Learn” colouring book was created to share evidence-based information about OI, tailored to young children, helping them better understand their condition. The goal of this work was to translate the English version of the book into Italian, making it accessible to audiences in different countries.

Methods: The Italian translation of the colouring book was done over approximately 5 months with the assistance of an interdisciplinary Task Force. Members of the aforementioned team included physicians, educators, students and researchers. Once the forward translation from English to Italian was complete, the manuscript was overseen by reviewers whom were tasked with revising and correcting any potential inconsistencies. Through myriad discussions and meetings, the book finally came together and was entirely translated to the Italian language.

Results: This study led to the creation of the book entitled “OI Coloro, OI Imparo”, which can provide an educational resource to Italian-speaking children affected by OI and their families, who may not have access to information adapted to their needs, age and culture. The book intends on empowering children with OI by providing an accessible and visually appealing resource that supports their learning about various aspects of living with OI, using iconography familiar to them.

Conclusion: This translated resource aims to support Italian children’s confidence, knowledge, and ability to navigate life with OI through evidence-based information. Future research includes modifying certain drawings contained within the book to represent the cultural norms/habits of Italy and translating the additional resources associated with OI Colour, OI Learn including the greeting cards, educational animated videos, colouring tote bags, etc.

Source of funding: The “OI Coloro, OI Imparo” project is supported by the Shriners Hospitals for Children-Canada.

Program CHHD

PI Argerie Tsimicalis

3-16 - Assessing Approaches to Measuring Interpersonal Physiological Synchrony between Dancers and Individuals with Dementia

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Background

Mouvement de Passage is a movement-based program that brings dancers into long-term care homes to foster connections with residents. The study followed the interactions between four residents living with advanced dementia and dancers over the course of eight weeks. Interpersonal physiological synchrony is a measure used to characterize the dynamic interaction of physiological responses between individuals and can provide valuable insights into nonverbal communication. The purpose of this project is to evaluate the feasibility of applying and adapting the existing interpersonal physiological synchrony pipelines, previously developed and used in the lab, to this study. If the adaptations appropriately account for the altered physiological signals in older adults with advanced dementia, then the synchrony measures will effectively capture meaningful physiological moments between residents and dancers.

Materials & Methods

Physiological recordings were taken using a wearable sensor placed on the fingertips of residents and dancers, measuring electrodermal activity (EDA), skin temperature (TEMP), and blood volume pulse (BVP). Open-source MATLAB scripts from the BIAPT lab's GitHub repository were used as the foundation for interpersonal synchrony analysis. These scripts were modified to accommodate the altered physiological patterns of older adults with advanced dementia. Different methods of preprocessing, such as filtering, detrending, and normalization, were evaluated to reduce noise while ensuring that meaningful physiological trends were preserved. Parameters of synchrony measures, single session index (SSI) and normalized symbolic transfer entropy (NSTE), were adapted and applied to the EDA and TEMP signals of opening and closing interactions for each session. Alternative methods were also explored for HR.

Results

A preprocessing pipeline was developed for EDA signals involving a 4th order Butterworth filter, normalizing the data across all opening and closing segments, and separating the phasic and tonic components to maximize the signal to noise ratio of the electrodermal activity signal. SSI was not suitable for analysis as it relies on long, continuous recordings and does not accommodate the shorter segments of the opening and closing interactions analyzed in this study. To address this, a sliding window correlation of 15 seconds was applied at the maximum cross-correlation time lag to detect moments of interpersonal physiological synchrony.

Conclusions

Evaluation of these measures will advance the overall scientific understanding of interpersonal connection in populations with limited verbal communication. Furthermore, this work will provide scientific insight into the impact of *Mouvement de Passage* on patients with dementia, bridging the gap between research and art-based practices.

Source of Funding

This study was funded by a Natural Sciences and Engineering Research Council (NSERC) Discovery Grant (RGPIN-2023-03619) awarded to Stefanie Blain-Moraes.

Program BRaIN

PI Stefanie Blain-Moraes

3-17 - Improving Coherence and Support in the AI-based MARVIN chatbot via Dynamic Short-Term Memory

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Introduction: The use of artificial intelligence (AI) in public health has grown rapidly in the past years, particularly through conversational agents like chatbots, which offer an efficient way to deliver personalized health information and engage users in meaningful dialogue. One example is MARVIN, an AI-powered HIV care chatbot whose development began in 2020, designed to provide people living with HIV (PWH) with information and guidance on antiretroviral therapy. Despite such advancements, many AI-based healthcare tools still struggle to express support and empathy towards users. This limitation mainly lies in their inability to preserve knowledge and maintain coherence across extended conversations. The following project addresses this challenge by developing and integrating a short-term memory module into MARVIN, with the goal of improving the chatbot's ability to deliver human-like conversations. Ultimately, this project aims to provide patients with a sense of familiarity and emotional support.

Methods: To address the need for more coherent and personalized conversations, we are currently developing a short-term memory module for MARVIN. This system is designed to dynamically summarize and retain key information shared by the user throughout the conversation. The chatbot will generate concise summaries using an open-source language model (Meta-LLaMa v3.1). After each exchange, the dialogue is first appended to the short-term memory. When the memory exceeds a predefined limit, a summarization step condenses the dialogue while preserving important details such as the user's medications or upcoming travel plans. This allows MARVIN to refer to previous information during a conversation and provide more personalized, context-aware responses, reducing the need for users to repeat themselves.

Results: As the project is still in development, no empirical results are available at this stage. However, once the short-term memory module is completed and integrated into MARVIN, we anticipate a significant enhancement in the chatbot's conversational abilities, particularly in maintaining coherence and continuity across extended interactions. Feedback from patient experts who tested the current version of MARVIN highlighted the need for memory integration, primarily to avoid having to repeat information during ongoing conversations. A future comparative evaluation, in which patient experts interact with both the memory-enabled and standard versions of MARVIN, is expected to demonstrate improvements in user experience, perceived empathy, and conversational fluidity.

Conclusion: Fostering empathy and understanding in AI-based chatbots is essential in healthcare to ensure patients feel heard and supported. This project addresses that need by integrating a short-term memory module into MARVIN, aiming to improve the quality of interactions for people PWH. By preserving conversational context, the chatbot is expected to deliver more coherent and human-like responses, enhancing patients' sense of connection and overall user experience. The next steps involve evaluating the impact of this memory integration through user testing with patient experts to assess improvements in perceived empathy, coherence, and satisfaction.

Source of Funding: This study was supported by the Unité Soutien SSA and RI-MUHC Internal Funding.

Program IDIGH

PI Bertrand Lebouché

9-07 - Development of a 3D Mechanical Stretch Device for Ligament Cell Stimulation

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Introduction: In sports and physically demanding jobs, ligament injuries are common, particularly to the anterior cruciate ligament (ACL). The typical repair technique is surgical reconstruction. However, it has several disadvantages, including lower mechanical characteristics, pain, instability, stiffness, and infection. Surgical repair often uses autografts or allografts derived from nearby tendons. Patients may find it challenging to return to their pre-injury activity levels due to these issues. Tissue engineering approaches are being investigated as a solution to these issues. One way is to create a three-dimensional mechanical stretch device that promotes ligament cell proliferation and differentiation. The purpose of this study is to design, build, and test a new 3D mechanical stretcher capable of correctly applying cyclical strain to ligament cells grown on novel elastic 3D printed scaffolds which may serve as a graft substitute.

Methods: The 3D mechanical stretch device was made using high-precision 3D printing technology in conjunction with computer-aided design (CAD) software, in collaboration with a researcher team in Poland. The device consists of a motorized system capable of applying controlled cyclical strain on scaffolds that have been seeded with cells. Human bone marrow-derived mesenchymal stem cells (hbmMSCs) were seeded into 3D-printed polylactic acid (PLA) scaffolds, Layform60, Layform40 and Layfelt. We are working with Dr. Wodarczyk in Poland to create a unique cyclical strain test apparatus for the scaffolds. The device's purpose was to simulate the physiological conditions that human ligaments face by applying mechanical strain in cycles. Cell growth and viability will be assessed using the LIVE/DEAD and AlamarBlue assays. Gene expression will be assessed using quantitative polymerase chain reaction (qPCR), with an emphasis on markers specific to ligamentous tissue, such as tenascin-C, scleraxis, and collagens I and III. Collagen I, III, tenascin-C, and scleraxis will be identified by protein expression analysis using immunostaining techniques.

Results: Experiments are currently ongoing, applying mechanical stretch to geometric variations of three-dimensional printed scaffolds. However, we hypothesize the cyclical strain (3-6% strain at 0.5 Hz) will significantly enhance the hbmMSCs' ability to survive, proliferate and differentiate on the scaffolds. We anticipate that tenascin-C, scleraxis, collagens I and III, and other significant ligamentous markers will be elevated in gene expression analysis, indicating successful tenogenic differentiation. Protein expression assays, on the other hand, should confirm the presence of scleraxis, collagen I, collagen III, tenascin-C, and collagen IV, supporting the differentiation of hbmMSCs into ligament-like cells. These hypothetical results would demonstrate how well the 3D mechanical stretch device functions to provide a physiological environment conducive to ligament cell activation and differentiation.

Conclusions: The development of the 3D mechanical stretch device represents a substantial advancement in tissue engineering for ligament graft substitutes. Although findings are still awaiting, we are confident that the device's ability to apply precise and regulated cyclical strain to cell-seeded scaffolds will improve ligament cell survivability, proliferation, and differentiation. This innovative approach may reduce recovery durations and enhance the mechanical properties of repaired ligaments, improving the outcomes of ACL reconstruction and other ligament repair procedures. Future research efforts will focus on improving the device's features and expanding its production for application in medicine.

Program SIS

PI Dr. Derek Rosenzweig

16-47 - Independent Association Between Vitamin D Insufficiency and Liver Fibrosis in People with HIV, regardless of Metabolic Dysfunction-associated Steatotic Liver Disease or Hepatitis C Coinfection

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BACKGROUND

Metabolic dysfunction-associated steatotic liver disease (MASLD) is the most common liver disease in people with HIV (PWH), who are also at high risk of liver fibrosis. Vitamin D insufficiency is prevalent in PWH and frequently observed in individuals with MASLD, yet its role in liver fibrosis progression in this population remains unclear.

METHODS

We conducted a multicenter cohort study involving PWH screened for hepatic steatosis and fibrosis using transient elastography. Hepatic steatosis was defined as controlled attenuation parameter ≥ 275 dB/m, and significant liver fibrosis as liver stiffness measurement ≥ 8 kPa. Vitamin D insufficiency was defined as serum 25-hydroxyvitamin D levels < 50 nmol/L. Incidence of significant liver fibrosis was assessed by survival analysis, and independent predictors were identified through logistic regression and generalized estimating equations modelling.

RESULTS

A total of 4,746 PWH were included (mean age 60.2 years, 72% men, mean BMI 25 Kg/m², 11% with diabetes, 23% with hepatitis C coinfection, 5% with hepatitis B coinfection, all on antiretroviral therapy) between 2014-2024. Vitamin D insufficiency was observed in 42% of participants, hepatic steatosis in 19% and significant fibrosis in 14%. At baseline, independent cofactors of vitamin D insufficiency included hepatitis C coinfection (adjusted odds ratio [aOR] 1.15, 95% CI 1.02-1.31), BMI (aOR 1.1, 95% CI 1.03-1.08), and hepatic steatosis (aOR 1.71, 95% CI 1.35-2.18) after adjusting for HIV duration, diabetes, CD4 cell count, parathormone levels, sex, and ethnicity. Over a median 7-year follow-up, the cumulative incidence of significant liver fibrosis was 17%, and significantly higher among PWH with vitamin D insufficiency (unable to attach the Figure). On multivariable generalized estimating equations models, vitamin D insufficiency was independently associated with development of liver fibrosis (aOR 1.44, 95% CI 1.14-1.80), adjusting for hepatic steatosis, diabetes, obesity, parathormone, CD4 cell count and HIV duration.

CONCLUSION

Vitamin D insufficiency is common in PWH, particularly in those with MASLD and hepatitis C coinfection. It is independently associated with the development of liver fibrosis, beyond traditional metabolic risk factors. These findings suggest a potential role for vitamin D supplementation in MASLD prevention strategies in PWH, possibly through anti-inflammatory and insulin-sensitizing mechanisms.

Program IDIGH

PI Giada Sebastiani

5-34 - Evaluating the impact of a knowledge translation tool for families affected by a leukodystrophy

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Introduction: Leukodystrophies (LDs) are a group of rare, inherited disorders that affect the white matter of the central nervous system. They are typically progressive, often leading to significant disability and premature death. For many families, the experience is made even more difficult by a lack of clear information about the disease, available treatments, and current research. One way to address this gap is through knowledge translation, the process of making research findings more accessible and useful to non-experts. The overarching goal of this study is to investigate how a knowledge translation tool, in the form of a brochure, can help parents of children with leukodystrophies better understand novel and future therapeutic options.

Methods: Participants were recruited from the MyeliNeuroGene Biobank and at the Leukodystrophies and Neurometabolic Disorders Clinic at the Montreal Children's Hospital between 2023 and 2025. Recruitment is ongoing.

Participants completed a demographic questionnaire, the Hospital Anxiety and Depression Scale (HADS), the University of Washington Self-Efficacy Scale, a stigma scale, and a custom questionnaire assessing disease knowledge and social exchanges. The custom questionnaire also included items on prior participation in disease-specific events.

Following the initial assessment, parents were asked to read a 60-page informational brochure focused on gene therapy and other novel treatments for LDs, then complete the same set of questionnaires. Wilcoxon signed-rank tests were used to assess differences between pre- and post-brochure responses.

Results: Of the twelve participants recruited, one was an individual affected by leukodystrophy, one was the wife of this participant and ten were parents of children with a leukodystrophy. Reported diagnoses among affected children included POLR3-related leukodystrophy, Aicardi-Goutières syndrome, and adrenomyeloneuropathy.

Wilcoxon signed-rank tests showed a significant reduction in total HADS scores following the brochure ($p = .017$, $r = .80$), indicating a large effect and meaningful decrease in psychological distress. Anxiety scores also significantly decreased ($p = .046$, $r = .67$). No significant changes were observed in depression scores ($p = .17$), in self-efficacy ($p = .23$), stigma ($p = .11$), social exchanges ($p = .61$), or disease knowledge ($p = .32$).

Conclusions: This is the first study to examine the impact of knowledge translation in families affected by leukodystrophies. Although post-brochure HADS scores decreased significantly, causality cannot be confirmed due to potential confounding factors (e.g., self-education, stressful life events). Disease-related knowledge, perceived self-efficacy, social exchange, and perceived stigma did not show significant improvement following exposure to the brochure.

The results from this study will be important to identify whether providing accessible information can improve parents' understanding, reduce uncertainty, and support informed decision-making. Findings may also help guide future initiatives aimed at improving communication, education, and support for families living with rare neurodegenerative disorders.

Source of Funding : This research was possible thanks to funding from the Montreal Children's Hospital Foundation (Estate of Daphne Dale Townsend), the Fondation Les Amis d'Elliot and the Canada First Research Excellence Fund, awarded to the Healthy Brains, Healthy Lives initiative at McGill University.

Program CHHD

PI Geneviève Bernard

7-43 - Simulating heterogeneous synaptic release: CV analysis under non-uniform conditions

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Background:

Long term plasticity is believed to be one of the underlying mechanisms of memory and learning, and determining whether plasticity occurred pre- or postsynaptically is crucial for understanding the underlying neural circuits. Neuroscientists often assume that the release probability in synapses follows a binomial model, where each release site has an identical release probability and quantal amplitude when studying long-term plasticity. With this simple assumption, it has been possible to elucidate whether plasticity is expressed by pre- or postsynaptic mechanisms using coefficient of variation (CV) analysis. However, studies present conflicting evidence regarding the assumption of uniformity across release sites. Some evidence shows that in biological models, synapses could exhibit heterogeneity. Such variation raises a critical question about whether CV analysis remains valid under more heterogeneous synaptic conditions. This project aims to address the question of synaptic heterogeneity by developing a computational framework to simulate synaptic responses and evaluate the accuracy of classical CV-based interpretations.

Methods:

An online JavaScript-based synapse simulator was developed to model evoked synaptic responses from two or three independently controlled release sites. Users can control the release probability (p_i) and quantal amplitude (q_i), allowing precise manipulation of heterogeneity of each site i . With each p_i and q_i value entered, the simulator will demonstrate a probability distribution of the release and calculate the mean, standard deviation, and CV of the release. Simulation batches were conducted by varying the number of release sites and the spread of p_i and q_i to investigate how CV changes with the overall mean. Plots were generated to compare the change of CV in homogeneous releases and heterogeneous releases and determine how increasing heterogeneity distorts the results of CV analysis.

Results:

CV is defined as the ratio of the standard deviation to the mean. The logic is that presynaptic changes affect only the mean, leading to changes in CV, whereas postsynaptic changes scale both mean and standard deviation proportionally, leaving CV unchanged. CV analysis is typically assessed by plotting normalized $1/CV^2$ versus mean. Data that fall along a horizontal line suggest postsynaptic expression, while deviations above (for LTP) or below (for LTD) a diagnostic line of slope 1 indicate presynaptic changes. However, under heterogeneous conditions, particularly when only one q_i was altered, the $1/CV^2$ vs. mean curve exhibited a sharp initial rise (or fall for LTD) followed by a plateau. Notably, only changing one of the p_i still allows for the data points to be correctly positioned above the diagnostic line. The linearity of CV also remains when both of the q_i change by the same scale.

Conclusion:

For postsynaptically expressed plasticity, classic CV analysis may eventually be effective with substantial mean changes, but it risks incorrect predictions with minimal mean changes due to the sharp rise when only one q_i changes, thus CV results under heterogeneous conditions should be interpreted with caution. However, the analysis remains valid for presynaptic changes.

Program BRaIN

PI Per Jesper Sjöström

9-03 - ARHGAP19 Function and Localization in Charcot-Marie-Tooth Disease

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¹Cancer Research Program

Introduction: ARHGAP19 is a small Rho GTPase-Activating Protein (GAP) which acts on RhoA, a key molecular switch for cellular pathways such as actin reorganization and cell division. ARHGAP19 negatively regulates RhoA by increasing its intrinsic hydrolase activity to promote hydrolysis of GTP to GDP, which inactivates the Rho GTPase. This 494-amino-acid protein plays a critical role in cell division, notably T-lymphocyte cytokinesis and Schwann cell development. ARHGAP19 has been found to be phosphorylated by kinases, such as CDK1 and ROCK at Thr404, Thr476 and Ser422 respectively. Three biallelic recessive nonsense mutations of ARHGAP19 - R394X, R407X and Q415X - have been identified in patients with motor-predominant hereditary neuropathies, which are grouped into Charcot-Marie-Tooth (CMT) disease. CMT is characterized by demyelination of neurons, which causes motor deficits in the lower limbs. The mutations cause a loss of the C-terminal phosphorylation sites, which potentially impedes proper ARHGAP19 localization to the nucleus. Moreover, these mutations lead to deficits resembling those with patients that have mutations inside the GAP domain of ArhGAP19, although the mechanism for how these variations lead to similar deficits remains to be explored.

Hypothesis and Goal: We hypothesize that the ARHGAP19 nonsense mutations (R394X, R407X, and Q415X), all located near the C-terminus of the protein, obstruct its ability to localize into the nucleus due to loss of residues Thr404, Thr476, and Ser422. The purpose of our research is to understand how the role and cellular localization of ARHGAP19 is disrupted in the three mutants. In the context of cortical neurons during embryogenesis, our objective is to understand the protein's negative regulatory effect on RhoA, which in turn tells us how it affects actin organization.

Methods: Our methodology consists of immunostaining from western blots with HEK-293 cells to validate expression from circular DNA plasmids of ARHGAP19 wild-type and mutants. Additionally, we assess cellular localization in N1E-115 neuroblastoma cells through immunofluorescence of the ARHGAP19 wild-type and mutants. To study the protein's role in developing neurons, we perform western blots and immunofluorescence of ARHGAP19 in DIV2 cortical rat neurons to determine its effects on motoneuron length and branching.

Results: Our preliminary results show that wild-type and mutants ARHGAP19 localize largely in the nucleus in N1E-115 cells. In addition, immunofluorescence reveals unique projections in the Q415X mutant, which may suggest partial cytoplasmic localization.

Conclusions: By understanding the role of ARHGAP19 and its truncated mutations in actin formation in cortical neurons, we can better understand CMT-associated neuropathies. Our initial observations do not support our hypothesis that mutant ARHGAP19 localization into the nucleus is disrupted. However, they give us a foundation to understanding how the protein mutations contribute to CMT.

Source of funding: NSERC

Program CRP

PI Nathalie Lamarche-Vane

6-35 - Low-Penetrance CEL-VNTR Frameshifts: A Potential Hidden Cause of Non-Autoimmune Diabetes

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¹MUHC

Background: Maturity-onset diabetes of the young (MODY) is a rare group of monogenic disorders characterized by dominant autosomal inheritance (~1% of all diabetes cases). Distinguishing MODY from autoimmune type 1 diabetes (T1D) has important therapeutic implications. Fourteen MODY genes have been identified and most of them are directly involved in beta cell function. However, the gene mutated in MODY8 (*CEL*) encodes a lipase secreted by the acinar cells of the pancreas. Mutations in *CEL* seem to damage beta cells due to proximity, and several patients with exocrine deficiencies develop diabetes before the age of twenty-five. *CEL* consists of 11 exons; the last contains a variable number tandem repeats (VNTR) region. Frameshift mutations in early VNTR repeats have been identified to cause MODY8, in addition to exocrine pancreatic symptoms.

Methods and hypothesis: In our ADDAM study (Accurate Diagnosis in Diabetes for Appropriate Management), a cross-Canada search for monogenic cases misdiagnosed as T1D, we found frameshift variants in the late *CEL*-VNTR repeats at higher frequency than expected. We hypothesized that these variants, cause diabetes at lower penetrance, which explains the absence of dominant family history (unaffected parents). As repetitive regions are incompletely captured by short exome reads, we further analyzed these variants by PCR and Sanger sequencing.

Results: To date, exomes of 350 patients have been analyzed. We found frameshift *CEL* variants in the late VNTR repeats of 21 patients, a prevalence of 6% in this select population, much higher than previously reported. All 9 frameshift-carriers that were additionally examined for VNTR length to date have the otherwise rare (1%) 12-repeat allele. By genotyping type 1 diabetic controls, the 12-repeat allele did not consistently carry the insertion — suggesting a more rare and potential pathogenic role to this frameshift.

Conclusion: If confirmed by further analysis and risk score calculations, results of this “agnostic” approach raise the possibility that, in addition to the rare known MODY8 form, the frameshift variants in the late *CEL* 12-repeat VNTR is likely pathogenic. We hypothesize that these hypomorphic alleles cause dominant diabetes with too low penetrance to be ascertained by family history in individuals with compromised beta-cell function. We predict that the genome of these cases will be enriched in variants known to affect beta-cell function.

Source of funding: CIHR

Program CHHD

PI Constantin Polychronakos

11 - Mitochondrial Dynamics Mediate Heat Stress Hormesis in *C. elegans*

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Background:

Hormesis refers to the biological phenomenon where exposure to a sublethal stressor, like a toxin or environmental factor, enhances an organism's ability to survive future stress. Although widely observed, the molecular mechanisms underlying hormesis are poorly defined. In *Caenorhabditis elegans*, mild heat stress increases resilience at subsequent stress and extends lifespan, potentially through mitochondrial remodeling and activation of stress-responsive signaling pathways. This study aims to dissect the roles of mitochondrial dynamics, such as fission and fusion, in mediating the beneficial effects of hormesis.

Methods:

Lifespan and stress survival assays were performed on wild-type worms and mutants defective in mitochondrial fission (*drp-1*), fusion (*fzo-1*, *eat-3*), and key stress pathways (*hsf-1*, *daf-16*, *atfs-1*, *hif-1*, *skn-1*, *ire-1*, *atf-6*, *pek-1*, *xbp-1*, *sek-1*). Hormetic heat stress was induced at 35 °C for 2 hours, followed by 24-hour recovery at 20 °C. Transcriptional activation was assessed using *hsp-16.2::GFP* reporter strains and quantified using fluorescence imaging. To complement experimental data, we reviewed RNA-seq datasets from recent heat stress studies and compared gene expression patterns with known transcriptional targets of stress pathways. Finally, RNAi screening of kinases will be used to identify upstream regulators essential for transcriptional responses and physiological benefits of heat stress hormesis.

Results:

Mild heat stress improved resistance to subsequent heat exposure and to various exogenous stressors such as anoxic, osmotic, and acute oxidative stress in wild-type worms. *Hsp-16.2* was expressed across all strains following heat stress, including mitochondrial dynamics mutants. However, *drp-1*, *fzo-1*, and *eat-3* mutants failed to exhibit increased stress resistance or lifespan extension following hormetic treatment, suggesting that mitochondrial dynamics are required for the functional benefits of hormesis. Comparative analysis of existing transcriptomic datasets supported the activation of conserved stress responses.

Conclusions:

Our findings demonstrate that mitochondrial dynamics are essential for the benefits of heat stress hormesis to occur. This work provides insight into the molecular mechanisms underlying stress resilience and longevity, with potential applications in aging research.

Source of Funding:

This research was supported by the Canada Summer Jobs program and funding from the Van Raamsdonk lab.

Program MeDiC

PI Jeremy Van Raamsdonk

5 - Validation and evaluation of Patient Decision Aids (PDA) for Women with Overactive Bladder (OAB) and Stress Urinary Incontinence (SUI)

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Introduction: Overactive bladder (OAB) and stress urinary incontinence (SUI) are the two most prevalent types of urinary incontinence affecting women in Canada. OAB is marked by a sudden, urgent need to urinate and is particularly common among frail older adults, often leading to falls, depression, and institutionalization. SUI, which affects up to 35% of adult women, involves involuntary leakage during physical activity. Some individuals experience both, known as Mixed Urinary Incontinence (MUI). Treatments for urinary incontinence are varied and range from lifestyle modifications and pelvic floor physiotherapy to medications, pessaries, and surgery. Treatment decision-making for urinary incontinence is highly individualized. Moreover, many first-line treatments are inaccessible or poorly tolerated, especially by older adults. As such, it is important to educate patients in order to facilitate shared-decision making. The first phase of this study was the creation of bilingual educational PDAs for the management of OAB and SUI respectively. The current phase of this study involves measuring the comprehensibility, acceptability, and desirability of PDAs using validated tools. Additionally, we will evaluate the PDAs impact on decision-making by assessing decisional conflict, and preparation for decision-making, using validated scales.

Methods: We aim to recruit 20 women with urinary incontinence (10 with SUI and 10 with OAB) from the clinics at CIUSSS ODIM and CHU Laval, where the PDA will be introduced as part of standard clinical care. Baseline data will be collected, including demographics, urinary incontinence symptoms, and comorbidities that could influence treatment decisions. Participants will use the PDAs and complete a questionnaire assessing their decision-making experience and the effectiveness of the tools using three validated tools: the Decisional Support Acceptability Scale (*DSAS*), the Decisional Conflict Scale (*DSC*), and the Preparation for Decision Making Scale (*PDMS*). Moreover, the Urinary Incontinence Short Form (*ICIQ-UI SF*) will be included in the survey to assess the severity and level of impact of the patient's incontinence. Following data collection, the results will be analyzed to determine the feasibility of PDA use in clinical practice, and to guide the refinement of the PDAs before broader implementation.

Anticipated Results: We are currently in the patient recruitment phase and aim to finish recruitment by the end of July 2025. We will start data analysis and PDA improvement in August 2025. We anticipate that the PDAs will improve patients' confidence in their treatment choices and reduce decisional conflict.

Conclusion: Currently available patient decision aids (PDAs) for OAB and SUI are limited in scope and structure, with none encompassing all treatment options for both conditions. This highlights the need for comprehensive, structured PDAs to support shared decision-making and improve the quality of care for patients with urinary incontinence. Ultimately, our study aims to both validate PDAs as a useful tool for the management of urinary incontinence and to improve the PDAs in response to patient feedback.

Funding: Medical Class of 1961 Summer Research Bursary for 2025 (\$3,200)

Program SIS

PI Maryse Larouche

14-35 - Analysis of the PBR and C-terminus domains of CdGAP in the nucleocytoplasmic shuttling of the protein in breast cancer cells

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Background: Cdc42 GTPase-activating protein (CdGAP), also named ARHGAP31, is a negative regulator of the small GTPases Cdc42 and Rac1, both GTPases promoting cellular motility through enhanced actin cytoskeleton dynamics. Recent studies have explored the effects of specific CdGAP mutations in the polybasic region (PBR). This PBR region, containing many basic amino acid residues such as lysines (K), plays an important role in mediating interaction with PI(3,4,5)P3. Furthermore, CdGAP binding with the transcription factor Zeb2 in the nucleus has been shown to repress E-Cadherin expression in a GAP-independent manner in breast cancer cells. Moreover, high CdGAP expression correlates with poor prognosis in all types of breast cancer. We hypothesize that CdGAP mutations lacking nuclear localization could have effects on its cellular functions, including cell migration, adhesion, or proliferation. This would allow the identification of new therapeutic targets, contributing to data needed in precision oncology.

Methods: HEK293, HEK293T, and MDA-MB-231 cells were cultured in DMEM + 10% Fetal Bovine Serum (FBS) + 1% Penicillin-Streptomycin (P/S). The cells were transfected with GFP empty vector, GFP-CdGAP full length and GFP-CdGAP PBRK_Q + K1310Q plasmid constructs. Immunofluorescence was performed with phalloidin-555 and DAPI staining. Cells were fixed with 4% formaldehyde, permeabilized with 0.25% Triton-X-100, blocked with 0.5% Bovine Serum Albumin (BSA), stained, and imaged. Boyden chamber migration assays were then performed. 2 x10⁶ HEK293 cells were suspended in serum-free DMEM medium and plated in the upper insert. Cells were allowed to migrate towards medium containing 10% FBS for 48h. Cells were then fixed, stained, and imaged.

Results and conclusions: In this study, the PBRK_Q + K1310Q CdGAP mutant was developed and analyzed to determine its cellular effects. We find that the PBRK_Q + K1310Q CdGAP mutant localizes exclusively in the cytoplasm in HEK293 and MDA-MB-231 cell lines. In addition, in a functional assay, we find that over-expression of PBRK_Q + K1310Q CdGAP mutant in HEK293 cells shows no significant difference in migration ability relative to over-expression with wild-type CdGAP.

This study confirms the lack of nuclear localization of the PBRK_Q + K1310Q CdGAP mutant in both HEK293 and MDA-MB-231 cells by immunofluorescence staining. These findings render the mutation a valuable tool for investigating the nuclear function of CdGAP. We will further utilize this mutant to conduct migration assay experiments in CdGAP-deficient MDA-MB-231 breast cancer cells. This study suggests a new avenue to further understanding the nuclear function of CdGAP, helping to define novel therapeutic strategies to treat breast cancer patients.

Source of funding: This project was made possible by funding from CIHR (PJT-180367).

Program CRP

PI Nathalie Lamarche-Vane

1-04 - Exploring Community Experts' Perspectives on the Feasibility of Promoting Foundations of Learning and Development (FOLD) Skills in Preschool-Aged Children

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Background: Developmental scientists have identified six Foundations of Learning and Development (FOLD) skills that are key to supporting lifelong learning and development in children. Evidence suggests that these skills (curiosity, creativity, critical thinking, self-regulation and executive function, perspective-taking, and internal representations of self) are highly valued by parents, educators, and other community members and recognized as essential for early childhood development and well-being. Yet further work is needed to understand the strategies, barriers, and facilitators that influence promotion of FOLD skills. This study aimed to explore community experts' perceptions of the feasibility and responsibility for promoting FOLD skills in preschool-aged children (3-5 years).

Methods: This study consists of a secondary analysis of data from the Streetlight Project, a phenomenological qualitative study exploring community experts' perspectives on the FOLD skills. Virtual in-depth interviews were conducted with 60 adults—parents, educators, clinicians, and early childhood care and education (ECCE) leaders—from urban and rural areas across 18 states and Washington, D.C. Interviews were conducted in English and Spanish. For this study, thematic analysis was used to identify themes related to the feasibility and responsibility of FOLD skill promotion in young children. Data analysis is ongoing.

Results: Of the 49 transcripts analyzed so far, 26 are from caregivers (mean age = 36.3 years [SD = 3.8]; 88% female; 69% with a graduate degree), 17 from educators (40.8 years [SD = 11.2]; 88% female; 100% with a graduate degree), and 6 from ECCE leaders (41 years [SD = 12.3]; 83% female; 67% with a graduate degree). Preliminary analyses reveal that across all respondents, promoting FOLD skills in preschool-aged children was seen as both feasible and necessary but requiring shared responsibility. Parents were identified as ideal primary promoters due to their emotional closeness and early involvement with their children, though many reported lacking the time, confidence, or resources to fully support skill promotion on their own. Educators and clinicians were seen as essential partners, supporting promotion of FOLD skills through school and clinical settings. ECCE leaders highlighted the need for consistent collaboration among families, educators, and communities. Ongoing analysis will explore clinician perspectives as well as differences in perceived feasibility and responsibility across contexts and respondent groups.

Conclusion: Preliminary findings show that promoting FOLD skills in preschool-aged children is both important and feasible when parents, educators, and community members work together. Respondents identified parents as the primary promoters of these skills but highlighted that active involvement from schools and community organizations is essential for consistent and effective skill promotion. These insights highlight the need for improved partnership among all early childhood community members to strengthen efforts to promote FOLD skills in young children.

Funding: The Streetlight Project was funded by a grant from the Esther A. & Joseph Klingenstein Fund via the Harvard Center on the Developing Child.

Program CHHD

PI Dr. Marilyn N. Ahun

6-36 - Study of Inflammatory Markers in Ugandan Neonates with Hypoxic-Ischemic Encephalopathy treated with Sildenafil

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¹RI-MUHC

I. Background

Hypoxic-ischemic encephalopathy (HIE) is a leading cause of neonatal morbidity and mortality worldwide, disproportionately affecting infants in low- and middle-income countries (LMICs), where access to advanced neonatal neurocritical care is limited. HIE occurs as a result of birth asphyxia, leading to insufficient oxygen and blood flow to the infant's brain and vital organs, and often causes long-term neurological impairment. While therapeutic hypothermia (TH) is the standard of care in high-income countries (HICs), its feasibility and efficacy in LMICs remain limited and uncertain.

II. Objective

This study investigates the inflammatory profile of neonates with HIE and evaluates the impact of sildenafil, a phosphodiesterase-5 inhibitor known for its neuroprotective and anti-inflammatory properties, as a potential adjunct therapy. The primary aim is to assess cytokine expression at baseline and following sildenafil treatment, in order to explore its modulatory effect on neuroinflammation in HIE. We hypothesize that sildenafil administration in neonates with HIE from Uganda modulates the inflammatory response, potentially attenuating neuroinflammation.

III. Methods

Neonates diagnosed with moderate to severe HIE were enrolled from a tertiary hospital in a low-resource setting. Blood samples were collected at predefined time points to measure concentrations of key pro- and anti-inflammatory cytokines. Sildenafil was administered at escalating doses following a Phase Ib open-label design. Cytokine profiles were analyzed to assess both baseline inflammation and post-treatment changes.

IV. Results

To be updated upon completion of data analysis.

V. Conclusion

This study seeks to provide insight into the inflammatory mechanisms underlying HIE and to evaluate sildenafil as a feasible, low-cost neuroprotective strategy. The findings may inform future clinical trials and contribute to the development of scalable interventions for neonatal brain injury where therapeutic hypothermia is not available or effective.

Program CHHD

PI Pia Wintermark

11-16 - Distinct Commensal Gut Bacteria Induce a Type 1 CD8⁺ T Cell Response

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Background: The gut microbiota plays an important role in shaping the host's immune system with alterations of this microbial community associated with diverse disease states ranging from IBD to neuropathology. Nevertheless, the immune reactivity of most bacteria residing in our intestine (i.e. commensal species) is not well-defined. Prior gnotobiotic mouse studies indicate that activation of CD8⁺ T cells, a cell subset critical for anti-pathogen and anti-tumor immunity, are selectively responsive to members of the gut microbiota community. To understand the mechanism(s) behind this selectivity, we developed an *in vitro* assay to measure responsiveness of CD8⁺ T cells to distinct commensal bacteria. Our results indicate that *Blautia* sp. YL58, a gram-positive bacteria, robustly induces interferon gamma (IFN γ) production by CD8⁺ T cells while a gram-negative commensal *E. coli* species (JM58) does not. Overall, our studies provide a reductionist, but scalable approach to investigating the diverse signalling pathways between our gut microbiota and immune system.

Methods: Cytokine production of *in vitro*-stimulated primary mouse splenocytes with bacteria and/or their supernatant were measured by ELISA and flow cytometry. Cellular mechanisms were investigated using immunophenotyping, transcriptional analysis, and co-culture systems of specific immune cells with heat-killed bacteria.

Results: Production of IFN γ by CD8⁺ T cells by *Blautia* YL58 stimulation is enriched in the CD44⁺ population within 24 hours of culture. By contrast, neither bacterial supernatant nor purified peptidoglycan stimulation was sufficient to phenocopy our results with co-culture with whole bacteria, despite the ability to induce cytokine production by bone marrow-derived macrophages. To expand our approach, we have partnered with Lallemand Health Solutions to test a panel of commercially available probiotics. We anticipate identifying additional strains or metabolites that activate CD8⁺ T cells and other immune cell populations with distinct effector functions. Mechanistically, T cell receptor-dependent vs. indirect myeloid cell involvement in bacterial sensing will be discriminated with the assays described above.

Conclusion: This project will expand our understanding of the immunomodulatory potential of specific commensal bacterial species, with a specific focus on type 1 CD8⁺ T cell responses.

Source of Funding: This project is supported by the Mitacs Accelerate Program in cooperation with Lallemand Health Solutions.

Program RESP

PI Irah King

1-05 - Disparities in neurodevelopmental disorders in children by primary spoken language: A comprehensive literature review

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Abstract

Background: Primary spoken language is a key social determinant of health and has been linked to disparities in child health outcomes, including neurodevelopmental disorders (NDDs). However, there is no comprehensive review on the association between primary spoken language and the risk of NDDs diagnosis in children.

Objective: To conduct a literature review of studies examining disparities in the risk and timing of NDD diagnoses among children by primary spoken language.

Methods: We searched PubMed, Scopus, and Web of Science for studies comparing the risk of neurodevelopmental disorders (NDDs) among children whose primary spoken language matched the official language of their country versus those with a non-official primary language. Primary spoken language included household language, parental spoken language, maternal mother tongue, or interview language preference. Eligible studies were published in English and included children under 18 years of age.

Results: Fifteen studies met the inclusion criteria, including cross-sectional (N=6), retrospective (5), prospective cohort (N=3), and ecological (N=1) designs. Fourteen were conducted in the United States, with one based in South Korea. Of these, nine examined the risk of NDDs only, three focused on the timing of diagnosis, and three addressed both outcomes. Ten of the fifteen studies (67%) reported significantly lower odds or prevalence of NDD diagnoses among children whose primary spoken language was non-official language of the country, compared to their peers with an official spoken language—mostly English— (adjusted odds/prevalence ratio range: 0.10-4.90), potentially reflecting underdiagnosis. Spanish was consistently associated with reduced or delayed diagnosis. Conversely, one study found higher NDD prevalence among children with non-official spoken languages—particularly Asian and African languages. Of six studies examining timing, 5 (83%) reported delayed diagnoses among children from non-official language households, while one found earlier diagnoses, potentially attributable to increased clinical vigilance or heightened parental concern.

Conclusion: Overall, the findings suggest significant disparities in both the risk and timing of NDD diagnosis associated with primary spoken language. Strengthening developmental surveillance and screening practices for children with non-official language may help to reduce disparities in diagnosis of NDDs.

Program CHHD

PI Ugochinyere Vivian Ukah, MPH, PhD

6-37 - Analysis of gene variations in the Longitudinal Natural History Study of Patients with Peroxisome Biogenesis Disorders.

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Introduction: Peroxisome Biogenesis Disorders (PBDs) are a group of inherited genetic disorders which impact peroxisome function. Peroxisomes are cellular organelles that regulate levels of important lipids and fatty acids. Consequences of PBD can include vision and hearing loss, adrenal dysfunction, liver and kidney disease, and leukodystrophy. The disease can manifest in a spectrum of severities, and there are no treatments. Currently there is no formal study that follows the progression of the disease, making it difficult to manage. To address this, our Longitudinal Natural History Study of Patients with PBD is constructing a retrospective database based on medical records of afflicted participants who are recruited worldwide. This summer we transferred our clinical data to an updated platform. The data was cleaned and supplemented it with new information. Lastly, we conducted several statistical tests to investigate genetic variations in participants.

Methodology: Data was moved from Microsoft Access to REDCap. Data cleaning included standardization of variable data points, renaming and restructuring of variables for clarity, and correction of missing or incorrect data. NCBI, HGVS, and ClinVar were used as references. Statistical analyses and corresponding figures were made using RStudio.

Results: Of 251 study participants, approximately 49% have variants in PEX1 and 16% have variants in PEX6. Of the 251 study participants, 118 had whole exome sequencing or peroxisomal disorder panels performed. Of these participants, 7 had variants in more than one peroxisomal gene. Of 251 study participants, 24 (9.6%) have at least one variant of uncertain significance (VUS). Of 194 unique cDNA variants, approximately 59% are missense. 158 of the 194 unique variants have a pathogenicity classification. Of these, approximately 72% are pathogenic, 15% have conflicting classifications of pathogenicity, and 14% are VUS.

Conclusions: During the transfer, the dataset was cleaned such that it was structured properly for statistical analysis. We ensured this was the case by successfully producing statistical results. We found that nearly half of the participants had variants in PEX1, consistent with the increased frequency of two alleles due to a population founder effect in persons of Northern European background. It should be investigated whether participants with multiple affected genes have exacerbated phenotypes as compared to other patients. Finally, functional testing could move VUSs to the pathogenic category to confirm diagnoses and enable prenatal diagnoses. Our results provide hypotheses for eventual research addressing the genetic basis of PBD. By developing a more accessible and comprehensive database, we advance towards our goal of developing guidelines for disease management, clinical endpoints for future interventional trials and data that can be used by the peroxisome community. With these measures we hope to enhance our understanding of PBD with the goal of improving outcomes for patients and their families.

Funding: CIHR, Mirum Pharmaceuticals

Program CHHD

PI Nancy Braverman

15 - Causal Plasma Proteins for Coronary Artery Disease and Aortic Stenosis

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Background: Coronary Artery Disease (CAD) and Aortic Stenosis (AS) are highly prevalent and life-threatening cardiovascular conditions. Thoroughly identifying and exploring their causal factors is critical for improving prevention and treatment. In addition, CAD and AS have significant patient overlap, presenting an important research direction: to identify their common and distinct causal proteins, which may provide evidence for specific therapeutic targets. However, separating causal proteins from all associated proteins remains an ongoing challenge. Developing fully adjusted proteomics models including comprehensive covariates, conducting Cox proportional tests for incidental cases, and incorporating genetic risk scores to refine causal inference may be practical solutions.

Methods: Using Olink proteomics data (2,916 proteins) within the European subset of the UK Biobank (n=35403, 3854 CAD cases, 393 AS cases), we conducted cross-sectional analyses for AS and CAD using univariate logistic regression models adjusted for age and sex. Subsequently, we incorporated BMI, hypercholesterolemia, hypertension, Type 2 Diabetes, and smoking as covariates in our model to minimize confounding. To eliminate confounding between the two target diseases, we removed all AS cases when testing for CAD associations and vice versa (219 overlapping samples). Furthermore, a Cox proportional-hazard model was employed to investigate proteomic associations within incidental cases. In addition, genetic risk scores (GRS) of CAD and AS were included as covariates and regressed directly with the protein levels to assess the relationship between the GRSes and plasma proteins.

Results: We identified 1101 significant proteins associated with CAD and 345 with AS when using univariate logistic regression. The fully adjusted model reduced the number of significant proteins to 391 for CAD and 24 for AS. We identified 247 significant proteins for CAD and 21 for AS in the Cox proportional-hazard test with fully adjusted covariates. Further examination removing overlapping samples yielded 362 significant CAD proteins after excluding AS cases, while only NT-proBNP remained significant for AS when excluding CAD cases. After adding GRS as a covariate, 38 proteins were no longer significant for CAD, and 30 new significant proteins were identified. For AS, 17 proteins were no longer significant and 2 new significant proteins were added. Linear regression analyses between GRS and plasma protein levels identified 145 significant proteins for CAD and 62 for AS.

Conclusion: The baseline model's large number of significant proteins (1,101 CAD; 345 AS) revealed severe confounding with collinear risk factors. Our multiple strategies, including a fully adjusted model, the cox proportional-hazard test, separating AS and CAD cases, and integrating GRS, sharply refined the list of associations and revealed potentially causal proteins by eliminating confounders. These approaches which integrate multiple approaches, provide greater sensitivity and the potential for deeper biological understanding of CAD and AS.

Program CHAL

PI James C. Engert

2-09 - Trends in Causes of Very Preterm Birth and Their Association with Neonatal Outcomes in Canada, 2018-2023: A Population-Based Cohort Study

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Background: Very preterm infants, born before 32 weeks of gestation, are highly susceptible to severe complications impacting their physiological systems. Different etiologies of preterm birth (PTB) likely lead to varying outcomes due to distinct pathophysiological mechanisms affecting fetal development. This study aimed to understanding these specific outcome profiles based on their PTB etiology, as they are crucial for refining clinical interventions tailored to each neonatal profile.

Methods: This retrospective cohort study used Canadian Neonatal Network data for 16733 infants born between between 23^{0/7} and 31^{6/7} weeks' gestational age (GA) from 2018-2023. Infants with major congenital anomalies, moribund status, or missing etiology data were excluded. Causes of PTB were categorized into four groups: chronic placental pathologies, acute placental events, spontaneous preterm labor (PTL) without preterm premature rupture of membranes (PPROM) (PTL-no-PPROM), and spontaneous PTL with PPRM (PTL+PPROM). The primary composite outcome included death prior to NICU discharge and/or major morbidity (bronchopulmonary dysplasia (BPD), severe neurologic injury (SNI), necrotizing enterocolitis (NEC), retinopathy of prematurity (ROP), and nosocomial infections (NI)). Multivariable robust Poisson regression models were used to calculate adjusted relative risks (aRR) with 95% CI using the PTL-no-PPROM as reference. Model 1 adjusted for GA and sex; Model 2 further adjusted for intermediate variables (outborn status, antenatal steroids, small for GA status and 1-minute Apgar).

Results: The mortality rate was: PTL-no-PPROM (8%, 603/7169), chronic placental (5%, 132/2556), acute placental (9%, 125/1423), and PTL+PPROM (7%, 380/5585). In the adjusted analysis accounting for GA and sex and using PTL-no-PPROM as reference (Model 1), mortality was higher in the placental chronic group (aRR 1.30, 95% CI 1.09-1.56) but did not differ significantly with other groups. Rate of mortality/morbidity was: PTL-no-PPROM (42%, 3009/7169), chronic placental (37%, 955/2556), acute placental (40%, 568/1423), and PTL+PPROM (39%, 2178/5585). In Model 1, mortality/mortality was higher in the placental chronic group (aRR 1.27, 95% CI 1.20-1.33) but did not differ significantly with other groups. Exploration of individual morbidities revealed distinct neonatal outcome profiles across etiologies. The chronic placental group had higher risks for BPD (aRR 1.55, 95% CI 1.44-1.66) and ROP (aRR 1.62, 95% CI 1.33-1.96), and a lower risk for SNI (aRR 0.53, 95% CI 0.43-0.66). Neonates in the acute placental group had a lower risk for NI (aRR 0.80, 95% CI 0.69-0.93). When adjusting of intermediate variables (Model 2), most associations between exposure and outcomes remained significant but were attenuated. The infants from the PTL+PPROM group had higher adjusted risk for BPD (aRR 1.07, 95% CI 1.01-1.13) and a lower risk of NI (aRR 0.83, 95% CI 0.76-0.92).

Conclusion: These findings demonstrate that PTB etiology is associated with distinct neonatal complication profiles. The association between chronic placental pathologies and the increase in BPD and ROP incidence is likely due to exposure to chronic antenatal inflammation, while the reduced risk of SNI correlates with rarer acute hemodynamic events seen in neonates born by cesarian section compared to PTL-no-PPROM. These results highlight the critical importance of adapting postnatal management strategies to PTB etiology.

Program CHHD

PI Marc Beltempo

16-49 - Detection of Acute Kidney Injury in Preeclampsia: A Comparison of Standard Criteria and Kinetic Estimated GFR (keGFR)

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Keywords: Hypertensive Disorders of Pregnancy; Preeclampsia; Acute Kidney Injury, Kinetic Glomerular filtration Rate

Background: Preeclampsia is a major hypertensive disorder of pregnancy that can lead to acute kidney injury (AKI). The current standard for diagnosing AKI, based on KDIGO (kidney disease: Improving Global Outcomes) criteria, relies on changes in serum creatinine (Cr) and may not capture early or transient changes in renal function. The kinetic estimated glomerular filtration rate (eGFR), a dynamic marker that includes creatinine kinetics, has been proposed as a more sensitive tool for early detection of AKI. This pilot study compares the incidence of AKI detected using KDIGO criteria versus keGFR in a small cohort of preeclamptic patients.

Methods: This analysis is a secondary review of data from 13 preeclamptic patients enrolled in the REVEAL study at the McGill University Health Centre between 2014 and 2015. AKI was defined using two methods: (1) the KDIGO criteria, defined as a rise in serum creatinine by $\geq 26.5 \mu\text{mol/L}$ within 48 hours or ≥ 1.5 times baseline within 7 days; and (2) a keGFR-based threshold, with AKI defined as $\text{keGFR} < 60 \text{ mL/min/1.73m}^2$.

To calculate keGFR, three creatinine values were used: one prior to admission (baseline), the first creatinine upon admission, and one subsequent inpatient value. The keGFR was calculated using the standard kinetic GFR formula. A cross-tabulation was performed to compare AKI classification between the two methods. Chi-square test was used to evaluate agreement and statistical significance.

Results: Using the Standard criteria, 1 of 13 patients (7.7%) was classified as having AKI. In contrast, keGFR < 60 identified 2 patients (15.4%) with AKI. One patient was detected to have AKI by both methods, while one additional patient was flagged only by keGFR. Chi-square analysis revealed a statistically significant difference between the two methods ($\chi^2 = 5.96$, $p = 0.015$), suggesting discordance in AKI detection.

Conclusion: In this cohort, keGFR identified a higher proportion of AKI cases than the standard KDIGO definition. Although both methods agreed in one case, keGFR detected an additional patient not captured by KDIGO criteria, possibly reflecting earlier renal dysfunction. These findings support the potential role of keGFR as a more sensitive indicator for AKI in preeclampsia. However, due to the small sample size, further studies with larger cohorts are warranted to validate these preliminary findings and assess the clinical utility of keGFR in obstetric care.

Program CHAL

PI Dr.Stella Daskalopoulou

15-44 - Activation of cardiac fibroblasts observed in TRPM7-deficient cells involves calpain signalling pathway

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Introduction: Transient Receptor Potential Melastatin 7 (TRPM7) is a cation channel bound to a kinase domain important for cellular Mg^{2+} homeostasis. We previously demonstrated that TRPM7 is cardiovascular protective and that TRPM7 downregulation is associated with cardiovascular inflammation and fibrosis. Here, we investigated underlying molecular mechanisms by studying hearts, and cardiac fibroblasts (CF) from wild-type (WT) and TRPM7-deficient mice (M7+/ Δ) focusing on calpain, a downstream target of TRPM7-kinase.

Methods: Hearts from wild-type (WT) and TRPM7-deficient (M7+/ Δ) mice were investigated for collagen deposition by Sirius red staining. Primary culture of CF from WT and M7+/ Δ were treated with calpeptin, a calpain-2 inhibitor ($10^{-5}M$) and investigated for protein expression of fibronectin, α -SMA and TGF β . Protein expression was investigated by immunoblotting.

Results: Hearts from M7+/ Δ exhibit increased collagen deposition (3.3% vs WT: 1.6%). CF from M7+/ Δ showed expression of TGF β 1 (2.14 ± 0.38 vs WT 0.25 ± 0.19), which was associated with increased fibronectin in CF M7+/ Δ vs WT (0.99 ± 0.18 vs 0.42 ± 0.12) and α -SMA (1.51 ± 0.13 vs 0.55 ± 0.99). CF from M7+/ Δ exhibited increased calpain-2 (1.55 ± 0.22 vs WT 0.55 ± 0.07), a known target protein of TRPM7-kinase. Treatment with calpeptin normalized expression of TGF β 1, fibronectin and α -SMA.

Summary and Conclusion: TRPM7-deficiency is associated with cardiovascular fibrosis. Cardiac fibroblasts from TRPM7-deficient mice exhibit increased fibrotic phenotype by mechanisms dependent on calpain activation. Additional experiments will define the interaction between calpain and TRPM7.

Program CHAL

PI Dr. Rhian M. Touyz

4-25 - The effects of glial glutamate uptake and lipid metabolism on sleep regulation

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Sleep is essential for life, which makes it important to understand. Many researchers focus on neurons, but increasing evidence is showing that glial cells are key regulators of sleep. Fruit flies (*Drosophila melanogaster*) are great models for such research, as they also sleep, and share many conserved genes linked to human sleep disorders. Their glial cells also share many similarities with mammalian glia. *Drosophila* astrocytes infiltrate synaptic regions, while ensheathing glia (ENS) wrap neuropil areas, and cortex glia (CTX) surround neuronal cell bodies. Our lab found that reducing the expression of a glutamate transporter protein called the Excitatory Amino Acid Transporter 1 (Eaat1) in ENS and CTX leads to sleep reduction. We also discovered that the expression of Eaat1 is correlated to the expression of factors related to lipid metabolism and the formation of lipid droplets (LDs). LDs are cellular organelles that store and release neutral lipids for energy production via beta-oxidation, and in the *Drosophila* CNS, they are primarily found in ENS and CTX. Previous studies have shown that disrupting lipid beta-oxidation affects sleep and leads to LD accumulation (Haynes et al., 2024). Thus, we hypothesize that Eaat1 regulates sleep by linking glutamate uptake to lipid metabolism and LD dynamics.

Candidate genes for an experiment are chosen via an RNA interference-based loss-of-function screening using the GAL4-UAS system. For sleep behavior analysis, we use a *Drosophila* Activity Monitor System (Trikinetics, Inc). This system works by adding a fly into a vial with food and a cotton plug on each end. Once added into the monitor, an infrared beam in the middle of the vial tracks the movement of the fly whenever it is crossed. If the line has not been crossed for 5 minutes, it is counted as sleep. To test whether the knockdown of sleep-regulating genes influences LD number or size, we dissect the brain and use Bodipy 493, which is a fluorescent chemical compound with hydrophobic properties, making it an excellent probe for neutral lipids in lipid droplets.

We proposed that in *Drosophila* CNS glia, the TCA cycle activity and fatty acid synthesis are supported by Eaat1-mediated glutamate uptake, facilitating LD formation. We then found that inducing lipolysis in cortex glia strongly promoted sleep, whereas impairing LD formation, thereby reducing lipolysis, in both ENS and CTX glia led to decreased sleep. These results suggest a metabolic pathway that connects glutamate and lipid metabolism to glial regulation of sleep.

Our research enables us to explore a novel metabolic pathway connecting glutamate and lipid metabolism to glial regulation of sleep.

This research project is supported by the CIHR and RI-MUHC.

Program BRaIN

PI Donald van Meyel

9-04 - Mlp60a and Sallimus are required to restrict branching of developing dendritic arbors.

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Regulating the growth and arborization of complex dendrites is crucial for the proper development of neural circuits. This dynamic growth is controlled by various proteins that regulate filamentous actin (F-actin). Spire, a *Drosophila* F-actin nucleation protein, has been shown by our lab to be essential for forming new dendrite branches in class 4 dendritic arborization (c4da) sensory neurons. However, the presence of Spire does not always predict new branch formation. To identify potential Spire-interacting proteins, we used mass spectrometry and identified Muscle LIM protein at position 60a (Mlp60a) and Sallimus (Sls), though neither has been previously linked to dendrite development.

Mlp60a is known for its role in F-actin crosslinking within muscle cell z-discs and is critical for myocyte development.¹ Our lab expressed Mlp60a::GFP in c4da neurons and found it localized to the nucleus and distinct puncta in dendrites. RNA interference (RNAi)-induced loss of Mlp60a in c4da neurons increased new branch formation, resulting in more terminal branches and greater total arbor length, both of which were suppressed in *spir* hemizygotes. This suggests an antagonistic relationship between Mlp60a and Spire.

Sls, also involved in F-actin crosslinking within z-discs, has a mammalian ortholog (Titin) which interacts directly with the Mlp60a ortholog (CSRP3) in cardiac muscle z-discs.^{2,3} This summer, we studied Sls expression in c4da neurons, and initial imaging of Sls MiMIC GFP lines indicated Sls presence within the cell body and arbor of c4da neurons. RNAi knockdown of Sls increased the number of terminal branches and total arbor length, mirroring the effects of Mlp60a loss and suggesting they may cooperate to restrict dendritic arbor branching.

Future experiments will explore the interactions between Spire, Mlp60a, and Sls on F-actin levels, distribution, and dendrite dynamics using live confocal imaging. By characterizing the novel roles of Mlp60a and Sls in dendritic development, we provide the first evidence of their function in the nervous system.

¹ Wishard et al., *Experimental Cell Research* 422:1, 2023. ² Knoll et al., *Cell* 111:7, pp. 943-955, 2002. ³ Knoll et al., *Circulation Research* 106:4, pp 695-705, 2010.

Program BRaIN

PI Donald van Meyel

6 - Characterization and Screening of Antimicrobial Candidates Against *Mycobacterium abscessus*

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Background: Non-tuberculous mycobacteria (NTM), particularly *Mycobacterium abscessus* complex (MABSC) and *Mycobacterium avium* complex (MAC), are increasingly recognized as severe opportunistic pathogens in Cystic Fibrosis (CF) patients. These organisms contribute significantly to lung function decline and are notoriously difficult to treat due to high resistance to available antibiotics and the toxicity of current treatment regimens. There is a critical need to identify new antimicrobial agents. The goal of this project is to evaluate novel chemical compounds for activity against NTM, with a focus on MABSC, to identify new therapeutic candidates.

Methods: Minimum inhibitory concentrations (MICs) of selected antibiotics were determined using the Resazurin Microliter Assay (REMA) against *M. abscessus* smooth and rough morphotypes. Assay quality and reproducibility were assessed through Z'-factor analysis. Bacterial isolates were cultured on solid media and prepared for experiments following PCR-based confirmation of strain identity. Preparations are conducted for high-throughput screening of two chemical libraries containing 20,000 unique compounds using an optimized 384-well format. Hits from the screening will be validated by REMA and then used to guide testing of promising compounds on clinical isolates derived from CF patients.

Results: MIC testing revealed varying susceptibility profiles across the rough and smooth morphotypes of *M. abscessus*. The REMA assay produced consistent data, supported by Z'-factor values within the acceptable range for assay robustness. All mycobacterial strains were successfully cultured, ensuring reliability of downstream application. Currently, compound screening plates are being prepared, setting the stage for drug screening.

Conclusion: This project supports the identification of new therapeutic agents against highly drug-resistant NTM species. We aim to contribute to the discovery of safer and more effective treatments for CF patients suffering from NTM pulmonary disease.

Source of Funding: This research was partly supported by the Canada Summer Job program.

Program IDIGH

PI Andreanne Lupien

9-05 - Development of astrocyte tiling in the mouse visual cortex

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Introduction: Astrocytes are glial cells in the central nervous system (CNS) involved in a wide range of neural functions, including synaptic transmission and plasticity. They interact with other CNS cells primarily through astrocyte processes, which extend to contact synapses and other glia. Through these processes, astrocytes influence neural activity through various mechanisms, such as neurotransmitter uptake and calcium signalling. In their mature form, astrocytes form tiles in the CNS, meaning they have non-overlapping processes with neighbouring astrocytes. Additionally, the maturation of astrocytes has been associated with visual cortex plasticity, particularly during the critical period of visual development.

Our lab previously investigated how properties of layer-5 visual cortex astrocytes change in development. A key finding was that the branches of young astrocytes extended further than those of old astrocytes, while the density of astrocytes remained the same. We therefore hypothesized that early in development, astrocyte arbours extend into the domains of neighbouring cells and then retract to form non-overlapping tiles in the mature brain.

Here, we test this hypothesis by performing stochastic multicolor labelling of visual cortex astrocytes followed by quantitative analysis of astrocyte volume overlap.

Methods: Four plasmids were designed using PiggyBac transposon system to each carry one of four fluorescent proteins, TagBFP, mTFP, EYFP, and mCherry, under an astrocyte-specific promoter, GFAP, and a plasma membrane-targeting sequence, Lck. CD1 mouse embryos underwent in-utero electroporation at ~E15 to target plasmid entry into cells in the visual cortex. This achieved relatively random expression of the four fluorophores in visual cortex astrocytes. Male and female CD1 mice underwent cardiac perfusion with 4% PFA between P3 to P50 and whole brains were extracted and cryopreserved. The brains were then cryosectioned into 50-µm-thick slices, with sections that contained the visual cortex immunofluorescence stained to enhance fluorophore detection. Using confocal microscopy, we identified neighbouring visual cortex astrocytes with different combinations of fluorophore expression and obtained 3D images of the cells. Using the Imaris software, we reconstructed individual astrocytes and quantified the overlapping region between neighbouring cells across development.

Expected results: We expect to find that visual cortex astrocyte overlap volume decreases over the course of development, such that neighbouring astrocytes of older mice have little-to-no overlap, while those of younger mice have overlapping processes. This research will expand our knowledge of how astrocyte morphology plays a role in visual cortex development, with potential clinical implications in studies involving the manipulation of visual critical periods.

Source of funding: This study was funded by the Canadian Institutes of Health Research and the Fonds de Recherche du Québec - Santé.

Program BRaIN

PI Jesper Sjöström

8 - Long-Term Multisystem Organ Damage Following Pregnancy-induced hypertension: Evaluating the Modifying Effect of Hypertension

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Background: Females with a history of Pregnancy-Induced Hypertension (PIH) may be at increased risk of developing organ damage later in life. However, few studies have evaluated the long-term impact of PIH on multiple target organs. Furthermore, it remains unclear whether new-onset hypertension modifies the relationship between prior PIH and organ-specific outcomes. This study aimed to evaluate the association between history of PIH and markers of brain, cardiac, vascular, and renal damage, and to determine whether new-onset hypertension modified these associations.

Methods: We analysed data from the UK Biobank, a cohort of individuals aged 40 to 69 years recruited across 22 UK centers between 2006 and 2010. We included females who had at least one live birth and for whom measurements of organ damage outcomes were available at baseline (2006-2010) or during follow-up (2014-2022). Organ damage was assessed using: urine albumin-creatinine ratio (uACR) for the kidney, volume of white matter hyperintensities (WMHs) for the brain, left ventricular ejection fraction (LVEF) for the heart, and pulse wave arterial stiffness index for the vasculature. Participants with a history of PIH diagnosed before baseline were matched to participants with normotensive pregnancies at a 1:4 ratio. Direct effect and effect modification of new-onset hypertension after PIH/first delivery and before follow-up were examined. Multiple linear regression models were used to assess the association between PIH and organ damage and test a potential new-onset hypertension effect modification.

Results: We identified a total of 955 females (191 with a history of PIH) with mean age 50 ± 7 years at recruitment. The mean duration between PIH and follow-up visit was 27.6 ± 10.9 years. New-onset hypertension was 27.2% in the PIH group and 16.5% in the control group. Females with history of PIH had slightly lower WMHs volume (2.9 vs. 3.4 mL), LVEF (57.2% vs. 57.3%), uACR ratio (1.7 vs. 1.9 mg/mmol) and higher arterial stiffness index (9.3 vs. 8.7), compared to females with history of normotensive pregnancies. In adjusted models, PIH was significantly associated only with increased arterial stiffness index ($\beta = 0.6$, 95% CI: 0.1-1.1). New-onset hypertension was associated with increased WMHs volume ($\beta = 1.6$, 95% CI: 0.7-2.4), but not with other outcomes. Interaction analyses showed no significant effect modification by new-onset hypertension.

Conclusions: A history of PIH was independently associated with increased arterial stiffness, but not with brain, cardiac, or renal damage. While new-onset hypertension was also associated with greater volume of WMHs, it did not modify the associations between prior PIH and any organ-specific outcomes. These findings highlight arterial stiffness as a key marker of organ damage after PIH and support the need for targeted vascular monitoring to inform early detection and risk stratification strategies in females with PIH.

Source of funding: We gratefully acknowledge the support of the Canadian Institutes of Health Research (CIHR) and of the Mach-Gaensslen Foundation, whose funding made this research possible.

Program CHAL

PI Louise Pilote

10-13 - Association of team composition in the delivery room with outcomes of very preterm infants - a prospective cohort study

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Introduction: Advances in neonatology and regionalized perinatal care have significantly improved survival and health outcomes among preterm infants born at less than 33 weeks' gestational age (GA). However, despite these advancements, more than 37% of these infants continue to experience major morbidity or mortality during hospitalization. The initial stabilization in the delivery room (DR) after birth is an important determinant of outcomes is influenced by the presence of highly qualified providers. However, there are no standards on what is a "highly qualified provider": a staff neonatologist (NN) or other trained personnel (clinical associates, nurse practitioners, trainees, etc.)

Objective: To assess the association of staff neonatologist NN presence in the delivery room DR with death or major morbidity among infants born <33 weeks' gestational age (GA).

Methods: This was a multicenter, prospective, cohort study of infants born <33 weeks GA in 14 tertiary-level NICUs (inborn) in Canada between 2020 and 2021. Data on infant characteristics, team composition and outcomes were obtained from the Canadian Neonatal Network database. Exposures were classified using based on the most senior provider present: no NN vs NN. Primary outcome was mortality or major morbidity (severe neurological injury, bronchopulmonary dysplasia, necrotizing enterocolitis, nosocomial infection, and severe retinopathy of prematurity). Odds ratios (OR) were estimated using multivariable logistic regression models adjusted for GA, antenatal steroids exposure, antenatal MgSO₄, rupture of membranes >24h, mode of delivery, multiple birth and small for GA, with generalized estimating equations to account for clustering within each site.

Results: Among 2492 infants included in the study population, 1071 (43%) had a NN in the DR. In the no NN group (N=1421), the most common senior providers were fellows (N=789). Overall, 95% (2355) of deliveries had ≥1 nurse and/or RT respiratory therapist. Rate of mortality/morbidity was 31% (435/1421) in the no NN group vs 46% (489/1071) in the NN group (adjusted OR 0.61, 95% CI 0.40-0.95). Sub-group analysis among infants born <29 and <26 weeks showed similar results (not shown).

Conclusions: The association between the presence of NN with worst outcomes (compared to no NN) in the DR is likely due to residual confounding by indication (NN select higher risk deliveries to attend) and site effect. This suggests that current interdisciplinary DR team models and supervision provide safe care in tertiary centers.

Source of funding: This research was supported by the Canadian Institutes of Health Research (CIHR), the Fonds de recherche du Québec - Santé (FRQS), the Montreal Children's Foundation, the Ministère de la Santé et des Services sociaux (MSSS), and the Canadian Neonatal Foundation.

Program CHHD

PI Dr. Marc Beltempo

5-28 - Promotion of Safe Activities for Children with Osteogenesis Imperfecta

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Background: Physical activity is essential for the overall health and well-being of individuals with *Osteogenesis Imperfecta* (OI), as it helps strengthen the bones and the muscles, but finding safe and appropriate activities for them can be challenging due to their unique physical limitations, fear of fractures and other health concerns (Francisca Galhardo Saraiva et al., 2024). While previous research has focused on the medical management of OI, a significant gap remains in resources that empower these children with safe, accessible physical activity while promoting social inclusion. This led to the development of an educational comic book, *Nicolas and the Badminton Challenge*. Geared for children aged 8-10+ with OI Type I, the story follows Nicolas, a resilient protagonist, in his journey to overcoming the challenges and discovering the joys of physical activity through adapted badminton. The engaging storytelling and colourful visuals not only serve to offer a relatable role model and practical guidance for children with OI to pursue active lifestyles, but also cultivate a culture of understanding among peers, educators and caregivers. Ultimately, the comic book seeks to transform societal perceptions, give actionable strategies for peers and educators in school and recreational settings, reduce isolation and empower children with OI to thrive in both physical and social realms.

Materials and Methods: An educational comic book for children with OI, their peers, and caregivers was developed through a collaborative process. The process involved identifying the need for child-friendly OI resources, gathering insights from patient partners and OI experts, attending training on knowledge translation and children's book writing, reviewing OI literature and researching modified sports for children with disabilities before selecting the appropriate sport. This groundwork led to the development of a narrative featuring a child with OI, which underwent rigorous critique from patient partners and OI researchers. leading in multiple revisions based on their input.

Results: "*Nicolas and the Badminton Challenge*" successfully integrated healthcare providers' insights, clinical accuracy, and child-centric storytelling to address challenges faced by children with OI. Key outcomes include clinical accuracy validated by professionals, improved accessibility through visual storytelling, promotes inclusivity with diverse character representation, offers adapted badminton guidance and interdisciplinary support with emotional resonance aligning with patient-reported challenges. This resource addresses OI's physical, emotional and social dimensions through engaging, clinically grounded storytelling.

Conclusions: A children's comic book was developed to address the gap between healthcare professionals and young patients with OI regarding physical activity. The comic, aimed at children aged 8-10 and their families, incorporates strength-based nursing principles to highlight patients' strengths and necessary qualities for overcoming daily obstacles. The storyline emphasizes perseverance in the face of challenges, particularly in physical activities. Future work could include updating the literature search, creating digital adaptations with animations, voiceovers or mini-games and developing diverse translations for cultural relevance.

Source of Funding: *Nicolas and the Badminton Challenge* is supported by Shriners's Hospital for Children®-Canada and Shriners's Summer Student Research Award

Program SIS

PI Argerie Tsimicalis

5-29 - Translating User Needs into Storytelling: Co-Creating Athlete Narratives for the ‘Teens OI’ eHealth Platform

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Background: 'Teens Taking Charge: Managing OI Online' (Teens OI) platform is being developed to meet the demand for transitional care and efficient self-management for youth with osteogenesis imperfecta (OI). As youth with this condition move into adult health care systems, this innovative eHealth program seeks to improve the quality of care during the transition (Tsimicalis et al, 2023). The study emphasized a user-centred design (UCD) approach that actively engaged parents and young individuals with OI throughout the design process, aiming to create a platform which meets their actual needs and preferences. Previous studies found that designing health solutions incorporating insights from users and stakeholders, would foster greater user engagement and enhance its overall effectiveness (Stinson, et al 2016). Preliminary results showed that youth with OI wished to learn through inspirational testimonials from peers with OI. Therefore, this work aimed to develop content that motivates them to remain active, tailoring the content to reflect their voiced needs.

Methods: The platform development applies a user-centred design (UCD) methodology guided by the 5 Elements of User Experience (UX) framework (Garrett, 2011). Initially, interviews with youth and parents, and focus groups with a council (health care professionals, individuals with OI, and a parent of a youth with OI) were conducted. These meetings focused on Garrett's Strategy and Scope plans and consisted of exploring participants' needs and pain points regarding transition. Following the analysis, subsequent interviews focused on Garrett's Structure, Skeleton, and Surface planes. Individuals with OI who had experience with physical activity were interviewed to share their stories. Additionally, one character was created based on a comic book about OI currently in development. The interview guide explored topics including motivation, learning process, resilience, perseverance, and empowerment, on how they engage in sports and overcome challenges.

Results: Insights from the interviews with youth (n=10), parents (n=6), and focus groups (n=6), showed that participants wanted to learn through different strategies, such as testimonials, text, images, pictures, and videos. Youth expressed their wish to learn from peer experiences through inspirational testimonials that emphasize how youth with OI achieved their goals, rather than solely highlighting outcomes. To address this need, we co-created the narratives of "OI Athletes", focusing on how they achieved their goals and remained active, highlighting their stories and testimonials, which reflect their experiences. Selection criteria for these stories included visibility within the OI community and relevance to youth interests so that the content resonates with the target audience. It consisted of four different athletes doing four different sports. The stories focused on swimming, para dancing, adapted badminton, and yoga. The stories were formatted for social media platforms such as Instagram and TikTok, which align with the media consumption habits of youth today.

Conclusion: The development of the Teens OI platform represents a significant step forward in addressing the self-management and transitional care needs of youth with OI. By sharing the stories of OI athletes and the different facets of their experience, such as vulnerability and resilience, teens can be inspired to embrace sport.

Program SIS

PI Argerie Tsimicalis

4-26 - INVESTIGATING THE ROLE OF MUCOSAL IgA RESPONSES IN SEX-BASED DIFFERENCES IN BLADDER TUMOUR DEVELOPMENT

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BACKGROUND: Bladder cancer (BC) displays notable sex-based disparities: males are approximately three times more likely to develop tumours, while females, though less likely to develop the disease, often present with more advanced and aggressive cases. The biological mechanisms underlying these differences remain poorly understood. Secretory immunoglobulin A (IgA), the most abundant antibody at mucosal surfaces, plays a key role in protecting these sites by binding and neutralizing antigens. However, its role in cancer remains complex: in male-dominated cohorts, higher intratumoral IgA levels have been associated with poor responses to standard treatments. In contrast, our unpublished analysis on TCGA data suggests a potentially protective role for IgA in females, pointing toward a sex-specific function that warrants further investigation. Sex-based differences in IgA secretion have been observed in other mucosal tissues, and estrogen receptors (ERs) have been shown to bind directly to regulatory elements within the immunoglobulin heavy chain locus. This suggests that IgA regulation may be influenced by sex hormones, potentially contributing to the observed disparities in bladder tumour development. However, IgA's role in the bladder mucosa remains largely unexplored, and no studies to date have investigated whether IgA expression patterns differ between sexes, or how such differences may influence bladder cancer outcomes. We therefore hypothesize that hormonally regulated sex-specific differences in IgA levels may contribute to differential bladder cancer progression between males and females.

METHODS: Twenty C57BL/6 mice, aged 12 months (10 males, 10 females), were exposed to the bladder-specific carcinogen N-butyl-N-(4-hydroxybutyl) nitrosamine (BBN), with half of each sex group receiving radiotherapy (RT; n=5 per group). Bladders were harvested and assessed for tumour presence using hematoxylin and eosin (H&E) staining. IgA expression and localization were analyzed by immunohistochemistry (IHC) and observed for presence and relative abundance with additional assessment focused on the urothelial layer to investigate potential IgA antibody transport via transcytosis.

RESULTS: Male mice exhibited a higher tumour incidence and developed larger tumours compared to females. Several tumour-negative bladders, particularly in females, displayed high IgA levels, supporting our hypothesis that IgA may play a protective role. However, a notable nuance emerged: IgA content appeared more closely associated with tumour status than with sex alone, as tumour-positive bladders across both sexes consistently showed low IgA levels. Given that ERs are known to bind regulatory regions of the immunoglobulin heavy chain locus, ongoing analyses are assessing estrogen receptor alpha and beta (ER α and ER β) expression to explore whether estrogen signaling may influence IgA niches in the bladder mucosa. Human bladder tissue is also being analyzed to determine whether similar patterns are observed across sexes in clinical samples.

CONCLUSION: This study addresses a significant gap in our understanding of sex-based immunological differences in bladder cancer. Our findings contribute to a growing but underexplored area of cancer immunology and may help inform future sex-specific therapeutic approaches.

SOURCE OF FUNDING: Canadian Urological Association - Bladder Cancer Canada Operational Grant.

Program CRP

PI Dr. Éva Michaud

10-08 - Alterations of brain metabolic profiles in young adult NICU survivors and healthy controls

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Background: Congenital heart disease (CHD) and preterm (PT) births are leading causes of infant morbidity and mortality. Survivors of these conditions commonly share neurodevelopmental challenges, including cognitive deficits, difficulties with executive functioning, motor impairments, and behavioural problems. Recent medical advances have improved survival rates for these two at-risk neonatal intensive care units (NICU) survivors. Nevertheless, they are experiencing neurodevelopmental deficits during their period of young adulthood, while the underlying mechanism of these challenges remains unclear. Recent evidence suggests that white matter (WM) dysmaturation may persist into young adulthood, providing insights into brain structural alterations that may result in long-term behavioral consequences. Another important aspect of understanding these WM dysmaturation is their biochemical profile. Using magnetic resonance spectroscopic imaging (MRSI), metabolites such as N-acetyl-aspartate (NAA), choline (Cho) and creatine (Cr) can be detected and associated with neuronal integrity and delayed maturation processes. However, there is no study to date investigating WM metabolic alterations in youth born with CHD and preterm.

Objective: Quantify and compare NAA, Cho and Cr WM absolute concentrations between youth born CHD, PT and healthy controls, using proton magnetic resonance spectroscopy (¹H-MRSI).

Hypothesis: We hypothesize that the youth born PT and with CHD will show reduced NAA levels, reflecting compromised neuronal integrity, and increased Cho and Cr levels, indicative of membrane turnover and delayed brain maturation.

Methods: We recruited three groups of participants, including youth born with CHD youth born preterm and age- and sex-matched healthy controls. ¹H-MRSI data was collected from the participants using a two-dimensional Point Resolved Spectroscopy (2D-PRESS) sequence. Tarquin software was used to calculate metabolite concentrations. WM voxels were selected using the FMRIB's Automated Segmentation Tool. Voxels acquired through the 2D-PRESS sequence that were included in subsequent analyses have mean WM volume fraction above 80%. Within these voxels, individual metabolite spectra, including NAA, Cho and Cr, were generated and then converted to absolute concentrations while only considering contributions from WM. After testing normality of the data distribution using the Shapiro-Wilk test, ANOVA tests were performed to compare metabolite concentrations between groups. A general linear model (GLM) was then applied to assess the potential effects of general variables (age, sex, BMI, SES and ethnicity) on the metabolite levels.

Results: A significant SES difference between was found between groups (p-value = 0.0023), with higher SES for controls compared to PT and CHD youth. No significant difference was observed for age, sex, BMI or ethnicity (p-value > 0.05), nor for metabolite concentrations. After controlling for relevant covariates such as age, sex, SES and BMI, no significant differences were found between three groups.

Conclusions: Young adults have exhibited different WM biochemical profiles than infants, with no significant difference between PT born, born with CHD and typically developing participants. These preliminary explorations suggest that evaluating metabolic alterations provides an avenue to acquire a fuller picture of the long-term effects of early-life adversity on the development of the brains of NICU survivors, which may provide a greater understanding of their persistent neurodevelopmental impairments.

Source of funding: Canada Research Chair program.

Program CHHD

PI Marie Brossard-Racine

2 - A systematic review on the association between pre-term and low birthweight with school readiness in children

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Abstract:

Background: Preterm birth and low birthweight (LBW) are well-established risk factors for early delays in development at preschool-age. However, the extent to which preterm birth and low birthweight affect school readiness - a critical milestone that predicts long-term educational and health outcomes- remains unclear.

Objective: This systematic review aims to synthesize current literature on the association between preterm birth and/or low birthweight and school readiness in children.

Methods: We searched MEDLINE, Embase, PsycINFO, CINAHL, and ERIC for relevant studies published in the databases from inception to June 2025. Eligible studies were those comparing school readiness between different gestational age at delivery or birthweight groups. We included studies that measured school readiness or its components (e.g., cognition, language, socio-emotional development, physical development, daily living) with a validated tool. Two reviewers conducted study screening, data extraction, and quality appraisal using the Newcastle-Ottawa scale for risk of bias assessment.

Results: Of 1226 articles screened, 15 studies (10 cohort studies, 3 studies and 2 case-control studies) were included in the review. Among the eligible studies, 10 examined pre-term vs term birth, 2 were on low birth vs normal birthweight, and 3 reported on both (of which 2 combined very preterm birth with low birthweight as a single exposure). There were 3 studies from Australia, 2 studies each from Canada, the United Kingdom, and the United States, and one study each from Finland, India, Italy, New Zealand, Poland, and Singapore. All studies found that children born preterm, especially those born very preterm, had a higher risk of low school readiness in at least one measured domain (odds or risk ratios of ≥ 1.4). Similarly, low birthweight was associated with lower school readiness, compared with increased or normal birthweight.

Conclusion: Preterm birth and low birthweight are significant risk factors of reduced school readiness, emphasizing the need for early developmental screening and targeted support for children born preterm or with low birthweight.

Program CHHD

PI Dr. Ugochinyere Vivian Ukah

12-23 - Effect of Hypoxia on Endothelial-to-Mesenchymal Transition in Placental Endothelial Cells

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Background: Endothelial-to-mesenchymal transition (EndMT) is a process where endothelial cells (ECs) lose their typical characteristics, leading to reduced vascular function, increased fibrosis, and impaired blood vessel formation. Preliminary data from Dr. Bertagnolli's lab shows that placental ECs exposed to hypoxia display signs of EndMT, including increased α -SMA expression, impaired tube formation, and preserved migratory capacity. We hypothesize that hypoxia, which is a hallmark of pre-eclampsia, a severe hypertensive pregnancy disorder characterized by placental dysfunction, maternal circulatory stress, and fetal growth restriction induces the upregulation of thrombospondin-1 (THBS1) in placental ECs. THBS1 is known to activate transforming growth factor-beta (TGF- β), which in turn initiates EndMT through either canonical or non-canonical signaling pathways. To assess whether THBS1 triggers EndMT via the canonical (SMAD-dependent) or non-canonical pathway, we will measure the expression of pathway-specific markers using RT-qPCR, Western blotting, and immunofluorescence. We will also assess the expression of SNAIL, VE-cadherin, and CD31 to confirm the phenotypic switch associated with EndMT in hypoxia-exposed placental ECs.

Methods: Primary placental ECs were cultured under normoxia (8% O₂, 24 h) or hypoxia (0.5% O₂, 24 h). THBS1 gene expression was quantified by RT-qPCR, using 18S rRNA as the housekeeping gene and the 24-hour normoxic condition as the calibrator. Relative quantification was calculated using the $2^{-\Delta\Delta C_t}$ method. THBS1 and SNAIL protein expression levels were assessed by immunofluorescence under both normoxia and hypoxia. Primary antibodies (1:100) were incubated overnight at 4°C, followed by secondary antibody incubation (1:1000) for 2 hours at room temperature. Fluorescence intensity was normalized to F-actin and quantified using MATLAB.

Results: RT-qPCR analysis showed a modest increase in THBS1 expression under hypoxia compared to normoxia. Further biological replicates are needed to confirm statistical significance. Immunofluorescence analysis supported this observation at the protein level, showing a marked increase in THBS1 expression under hypoxia (5.0 ± 1.8) versus normoxia (1.6 ± 0.4). Notably, SNAIL protein expression, a key downstream effector of TGF- β signaling and a known driver of EndMT, was significantly elevated under hypoxia (0.3 ± 0.1) compared to normoxia (0.006 ± 0.003).

Conclusions: These findings suggest that hypoxia-induced upregulation of THBS1 may enhance TGF- β signaling, promoting SNAIL expression and subsequent EndMT in placental endothelial cells. To investigate whether this process is mediated through THBS1-dependent activation of TGF- β , upcoming experiments will involve treating cells with 30 μ M LSKL peptide, a specific inhibitor of THBS1-mediated TGF- β activation, or with 30 μ M SLLK peptide as a scrambled control. These studies aim to clarify the role of the THBS1-TGF- β axis in driving EndMT and to evaluate THBS1 as a potential therapeutic target for placental vascular dysfunction in pre-eclampsia. Future work will focus on identifying the specific TGF- β signaling pathways activated by hypoxia that contribute to this phenotypic transition.

Source of Funding:

Summer fellowship award from the Centre for Research in Reproduction and Development (CRRD).

Program CHAL

PI Mariane Bertagnolli

11-18 - Bioengineering 3D Intestinal Co-Culture Model as a Therapeutic Screening Platform for Inflammatory Bowel Disease

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Background: Inflammatory bowel disease (IBD) is a chronic condition characterized by persistent inflammation of the gastrointestinal tract, primarily including Crohn's disease and ulcerative colitis. While various therapeutic strategies exist, patient responses vary widely, necessitating more personalized treatment approaches. Traditional 2D in vitro models and animal studies fail to fully replicate the complexity of human gut inflammation, underscoring the need for more physiologically relevant models. This study aims to develop a 3D co-culture model that mimics the intestinal microenvironment to assess inflammatory responses and evaluate potential novel therapies for IBD.

Methods: A 3D co-culture system was engineered using HT-29 intestinal epithelial cells and IRM-90 fibroblast cells. The model consisted of gut epithelial cells embedded within an alginate-gelatin hydrogel, while fibroblasts were seeded onto an electrospun PLA mesh resembling collagen matrix. The cell lines were first assessed for cell viability, metabolic activity, and proliferation. Inflammation was induced using lipopolysaccharide (LPS) to stimulate an immune-like response, followed by treatment with dexamethasone, a corticosteroid with anti-inflammatory effects. The model's inflammatory response was assessed by measuring TNF- α and IL-1 β cytokine levels. Finally, longer term (2-4 weeks) of co-culture was initiated in the interface model of gel/electrospun scaffold, and epithelial cell polarization was assessed.

Results: The 3D co-culture model exhibited sustained cell viability and metabolic activity, confirming its stability as a platform for studying gut inflammation. Upon LPS stimulation, TNF- α and IL-1 β levels significantly increased, indicating a successful inflammatory response and validating the model's ability to mimic IBD-like conditions. Following dexamethasone treatment, cytokine levels decreased, demonstrating the model's responsiveness to therapeutic interventions. Co-culturing HT-29 cells with fibroblasts demonstrated the model's capacity to replicate critical cellular interactions characteristic of the intestinal microenvironment. The compartment model consisting of fibroblasts on the electrospun mesh did not clearly induce epithelial cell polarization in the gel compartment.

Conclusions: This 3D bioengineered gut model provides a reproducible and scalable platform for investigating inflammatory processes in IBD and screening potential therapeutics. The ability to induce and reverse inflammation within this model supports its application in personalized medicine. Additionally, the model could be adapted for use in gut-on-a-chip systems, further enhancing its translational application in clinical research as effective and targeted therapies for IBD. Future research will investigate how fibroblast interactions influence the apical-basal polarity of epithelial cells. By comparing hydrogel-embedded and direct co-culture models, we aim to identify the optimal conditions for preserving intestinal integrity.

Program SIS

PI Derek Rosenzweig

12-24 - Benchmarking detection of DNA copy number variation using high-density methylation microarrays

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Introduction

SNP arrays are considered the gold-standard in the detection of DNA copy number variants (CNVs), with mature algorithms assisting in their detection. It has also been proposed that high-density methylation arrays can also be used for this purpose, because the total signal intensity of methylation probes correlates with DNA quantity. Multiple packages have been developed in R programming language for this purpose, mostly utilizing the circular binary segmentation algorithm. The algorithmic accuracy compared to SNP arrays have not been fully explored however in leiomyosarcomas (tumors characterized by extensive genomic instability), which is the objective of this project.

Methods

Tumor-matched SNP array data and methylation data from 10 cases of leiomyosarcoma was retrieved from the NIH Genomic Data Commons (GDC). The processed data from GDC was used to retrieve log2 ratios from SNP array data, which were then used to detect CNVs using < -0.2 and > 0.2 as cut-offs for deletions and amplifications, respectively.

CNVs spanning less than 100 probes were excluded from analysis to reduce bias. For the methylation data, they were processed using ChAMP, Conumee, Epicopy, Sesame and MethyLMaster packages in R.

Results

The number of CNVs from the SNP data are counted and binned into the affected chromosomes. These datapoints are then compared to the results from the algorithms that identify CNVs in the methylation data, and these results are assigned into the same bins. This data will now be compared to methylation data-generated CNVs by accounting for the:

1. accuracy of the estimation around the locus of the generated CNV, by providing the weighted mean of the accuracy from probes in that region,
2. number of CNVs identified on each chromosome.

Conclusion

This project seeks to quantify the accuracy of the algorithms developed for detection of CNVs from the methylation-based array data. We address this problem by analyzing tumors characterized by extensive chromosomal instability, such as leiomyosarcoma. We evaluate the accuracy of CNV calling from methylation data by comparing CNV outputs to those produced by the current gold-standard of SNP arrays. Identifying the most accurate method, therefore, will enable further processing of pre-existing methylation data, thereby providing a wealth of CNV data which can be used for further sarcoma research.

Program CRP

PI Joanna Przybyl

5-30 - Quality of Life and Stress in Families Affected by a Leukodystrophy: A Longitudinal Study

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Introduction: Leukodystrophies are a group of rare, inherited disorders affecting the brain's white matter. These conditions are often progressive, leading to increasing disability and frequently premature death. While the clinical burden of leukodystrophies is well recognized, the psychosocial impact on families remains poorly understood. To date, no studies have examined these longitudinally.

This project aims to prospectively investigate parental stress and QOL in families affected by leukodystrophies, and how they relate with patient's clinical symptoms and functional status. We hypothesize that parental stress and QOL will correlate with clinical features, life stressors, and functional scales over time. Furthermore, we expect that parental stress will vary by leukodystrophy subtype, with more rapidly progressive diseases associated with higher stress levels, and that mothers will report higher stress and lower QOL scores than fathers over time.

Methods: Parents of children diagnosed with leukodystrophies were recruited between 2014 and 2025. Parents completed the PedsQL™ Family Impact Module (FIM), the PedsQL™ Generic Core Scales Parent Proxy Report, the Parenting Stress Index (PSI) or the Stress Index for Parents of Adolescents (SIPA), and a demographic questionnaire. Clinical data, including the presence of eight clinical features and five functional scales (i.e., Gross Motor Function Classification System, Gross Motor Function Classification - Metachromatic Leukodystrophy, Manual Ability Classification System, Eating and Drinking Ability Classification System, and Communication Function Classification System) were also assessed. Questionnaires and clinical assessments were administered in person, electronically, or via email every six months to one year. Three timepoints per participant were used for analysis. Non-parametric tests (Friedman, Mann-Whitney U, Wilcoxon) were used to analyze changes over time, group differences, and comparisons to norms. Analyses were conducted with SPSS.

Preliminary results: A total of 65 parents (45 mothers, 20 fathers) of 49 children (33 males, 16 females) completed at least three questionnaires over the study period. The FIM was the most frequently completed measure, with response rates of 90% (mothers) and 81% (fathers). Most parents (91% / 90%) were married or living common-law; 69% of mothers and 75% of fathers were employed. Among 19 molecular diagnoses, the most common were POLR3-related leukodystrophy, Aicardi-Goutières syndrome, and X-linked adrenoleukodystrophy; five children lacked a molecular diagnosis. No significant percentile changes were observed over time for the Family Impact Module (n = 62) or PedsQL scores (n = 26). Mothers and fathers showed similar Family Impact Module scores. The Parenting Stress Index revealed parental stress levels were significantly above average (Mdn = 69.0; W = 301, p = 0.001, r = 0.63), but did not vary significantly across timepoints (n = 26).

Conclusions: Preliminary analysis indicates that family impact and parental stress levels remain stable over time, with parents experiencing consistently elevated stress compared to normative levels. This underscores the importance of ongoing support for families managing chronic conditions. Ongoing analyses will assess how stress and QOL evolve with clinical progression and leukodystrophy subtype.

Source of Funding: This study is supported by the Montreal Children's Hospital Foundation (Estate of Daphne Dale Townsend) and the Fondation Les Amis d'Elliot.

Program CHHD

PI Geneviève Bernard

3-19 - Euthyroid Pretibial Mucinous Dermatoses: A Systematic Review of Current Evidence and the Controversy Surrounding Their Classification

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Background:

Cutaneous mucinoses are broadly classified as primary or secondary and further subdivided as localized or generalized based on clinical distribution. Pretibial myxedema, classically seen in Graves' disease, is a typical example of secondary localized mucinosis. However, reports have described similar lesions in euthyroid individuals with no history of Graves' disease, particularly in those with other thyroid dysfunction, morbid obesity, venous stasis, or chronic lower extremity lymphedema. This has led to the proposed diagnoses of obesity-associated lymphedematous mucinosis (OALM) and stasis mucinosis, though some authors suggest these may represent a spectrum of the same condition. We describe a representative case followed by a systematic review of the literature on euthyroid pretibial mucinous dermatoses.

Methods:

We conducted a systematic review to summarize existing evidence on this underrecognized entity. A comprehensive search of PubMed, Embase, Web of Science, and MEDLINE was conducted from inception to May 20, 2025, following the PRISMA guidelines. The study was registered in PROSPERO (CRD420251081183). Study quality was assessed using the Oxford Centre for Evidence-Based Medicine 2011 criteria.

Results:

A total of 24 studies met the inclusion criteria, describing 38 patients. The mean age was 65 ± 13 years, and 50% were female. All patients were euthyroid at the time of diagnosis. Only 3/38 had any clinical or serologic evidence suggestive of subclinical Graves' disease despite euthyroid status. This was identified as having one of the following: abnormal thyrotropin receptor autoantibody, absent response to thyrotropin-releasing hormone stimulation test, or exophthalmos, either at presentation or on follow-up. The remaining 92% (35/38) had no history or signs of Graves' disease.

The most common clinical presentation was bilateral, chronic, gradually progressive lower leg edema, ranging from pitting to non-pitting, accompanied by indurated skin with translucent, erythematous, or pigmented papules, nodules, or plaques, often with an overlying peau d'orange texture. A unilateral presentation was described in three patients. Morbid obesity was the most common risk factor, present in 55% (21/38) of cases, followed by venous stasis and other contributors to chronic lower extremity edema or lymphatic obstruction.

The most effective management strategies involved addressing underlying risk factors such as obesity, edema, or venous stasis, using interventions like lifestyle modification, weight reduction, and gradual compression therapy. Mid-to-high potency topical corticosteroids and monthly intramuscular triamcinolone injections were commonly used for cutaneous symptoms and led to clinical improvement.

Conclusion:

OALM and stasis mucinosis are underrecognized mimics of Graves' dermopathy. Clinicians should consider these entities in patients with bilateral lower extremity edema and mucinous skin changes in the absence of thyroid disease. Early recognition and targeted management addressing underlying risk factors and cutaneous symptoms are essential to improving outcomes.

Program CRP

PI Dr. Ivan V. Litvinov

3-18 - Efficacy of Upadacitinib for the Treatment of Alopecia Areata: A Systematic Review and Meta-Analysis

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Background:

Alopecia areata (AA) is a chronic, immune-mediated disorder characterized by non-scarring hair loss due to cytotoxic targeting of hair follicles. Several JAK inhibitors, including baricitinib, deuruxolitinib, and ritlecitinib, are approved for severe AA (SALT ≥ 50). Upadacitinib, a selective JAK-1 inhibitor approved for atopic dermatitis, has shown off-label promise in AA, particularly in patients with comorbid inflammatory conditions. However, a comprehensive synthesis of its efficacy, safety, and clinical outcomes in AA is lacking. This systematic review evaluates existing evidence regarding upadacitinib in the management of AA.

Methods:

We conducted a systematic review following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to evaluate the efficacy of upadacitinib for AA. The study protocol was registered on PROSPERO (CRD420251082709). Embase, Web of Science, MEDLINE, and PubMed were searched from inception to June 22, 2025. Two reviewers independently screened articles, extracted data, and assessed quality using the Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence. Of 221 unique records, 26 studies met inclusion criteria, all reporting SALT score changes following upadacitinib treatment.

Results:

A total of 118 patients were included in the meta-analysis (mean age [SD]: 26.4 [$\pm$ 9.6] years; 55.1% female). The pooled mean SALT score reduction was 60.8% (95% CI: 46.3-75.3; $p < 0.000001$, $I^2 = 90.3\%$). Doses ranged from 7.5 mg to 30 mg daily, with a mean treatment duration of 39.4 ($\pm$ 25.2) weeks. Overall, 67.8% achieved SALT50, and 19.5% achieved SALT100. Approximately one-third of patients transitioned to upadacitinib following prior JAK inhibitor use, primarily due to suboptimal therapeutic response and comorbidity management. The most common indication for upadacitinib initiation was concomitant atopic dermatitis with AA. Adverse events occurred in 29.0% ($n=34/118$) of patients, all of which were mild and did not result in treatment discontinuation.

Conclusions:

JAK1 inhibition with upadacitinib appears to be a promising treatment modality for patients with moderate-to-severe AA, including those with prior JAK inhibitor exposure. Its established efficacy in other dermatologic conditions supports its use in patients with comorbidities for which upadacitinib is already approved. However, the current evidence is limited by small sample sizes, significant heterogeneity, and the predominance of lower-level studies. Large-scale, controlled trials are needed to validate these findings and identify predictors of treatment response.

Program CRP

PI Ivan Litvinov (co-PI)

8-48 - Investigating novel SH2 domain binding phosphotyrosine residues from pathogenic variants of cancer and Mendelian diseases

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Src homology 2 (SH2) domains are critical protein-protein interaction modules that mediate signal transduction by specifically recognizing phosphorylated tyrosine residues (Yaffe 2002). These signaling pathways regulate essential cellular processes (Bell and Ryan 2005) and are implicated in a number of diseases, including cancer, lipid metabolism disorders, and genetic disorders (Martin 2003; Benito-Vicente et al. 2018; Sassone-Corsi and Borrelli 1992). Although SH2 domains have been extensively characterized, their regulation by genetic variants, particularly those introducing novel SH2-binding motifs, remains poorly understood. Furthermore, the functional consequences of such mutations are largely uncharacterized but can be explored using emerging technologies like protein domain microarray (Chen, Sagum, and Bedford 2020).

In this study, we hypothesized that disease-associated genetic variants may alter cellular signaling by creating novel phosphotyrosine sites that engage interactions with SH2 domain (**Fig. 1**). To identify such tyrosine-generating variants, we performed a bioinformatic analysis of public databases for cancer hotspot mutations via Cancer Hotspots database (Chang et al. 2016) and Mendelian variants via ClinVar database (Landrum et al. 2025) (**Fig. 2A**). This analysis revealed six tyrosine-generating variants: four cancer hotspot mutations and two Mendelian variants. Four cancer hotspot mutations identified were FLT3 D835Y from AML, AR H875Y from prostate cancer, ERBB2 D769Y from breast cancer, and ERBB3 D297Y from breast cancer. Two Mendelian variants identified were PCSK9 D374Y from hypercholesterolemia and UMOD C106Y from autosomal dominant medullary cystic kidney disease (**Fig. 2B**). To validate whether phosphorylation at these novel tyrosine residues induces new SH2 domain interactions, we assessed their binding using a protein domain microarray (Chen, Sagum, and Bedford 2020) (**Fig. 3A**). Phosphopeptides were derived from AR H875Y (**Fig. 3B**), ERBB2 D769Y (**Fig. 3C**), FLT3 D835Y (**Fig. 3D**), and PCSK9 D374Y (**Fig. 3E**) for this assay. These variants generated novel SH2 domain binding sites that were not observed in their respective wild-type or non-tyrosine variant forms. Notably, the strongest SH2 domain-binding signals were observed for PIK3R1/2/3_N in FLT3 D835Y; SHC1/3, SOCS7, and TNS4 in AR H875Y; FES, FGR, FYN, and SHC1/2/3 in ERBB2 D769Y; and RASA1, PIK3R2, SOCS7 in PCSK9 D374Y. To further validate phosphorylation at these tyrosine sites under in vitro or in vivo conditions, we reanalyzed the public phosphoproteomics database (PRIDE) (Perez-Riverol et al. 2025) for corresponding phosphopeptides (**Fig. 4A**). Among the four variants, we confirmed phosphorylation at FLT3 D835Y in an AML cell model (Perez et al. 2019) (**Fig. 4B**).

Finally, we are introducing the variants into plasmid vectors via site-directed mutagenesis to evaluate their functional impacts. We aim to overexpress them in cell lines using lentiviral transduction, assess the resulting phenotypic changes, and investigate changes in downstream gene expression to uncover potential mechanisms (**Fig. 5A**). In particular, we plan to overexpress wild-type PCSK9 and its D374Y variant in HeLa cells to determine whether this variant affects LDL uptake (**Fig. 5B**) by gene profile regulation (**Fig. 5C**).

Overall, this study offers new insights into how disease-associated variants that alter SH2-binding motifs can rewire signaling networks, providing a foundation for uncovering novel regulatory mechanisms in disease and potential therapeutic targets.

Program CRP

PI Dae-Kyum Kim

2-14 - Hippocampal Development and Its Relation to Executive Function in Adolescents and Young Adults Born Very Preterm and with Congenital Heart Disease

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Background Children who survive early-life medical adversities, including very preterm (PT) birth or congenital heart disease (CHD), frequently face persistent challenges in executive function (EF). EF refers to higher order, cognitive abilities crucial for adaptive behaviour, decision-making, and self-regulation. Among brain structures potentially underpinning these EF difficulties, the hippocampus stands out due to its heightened vulnerability during late gestation and infancy, when these children are exposed to hypoxic-ischemic injury and systemic inflammation. Although prior research separately documented hippocampal volume reductions in PT and CHD survivors, direct comparisons at the subfield level remain scarce. This gap is significant, as subfield-level analyses may uncover region-specific vulnerabilities otherwise obscured by global measures. This study sought to determine whether early-life medical adversities differently alter hippocampal subfields, and whether those hippocampal alterations are associated to EF impairments.

Methods In this study, we enrolled participants aged 16-27 years across three groups: PT, CHD and healthy controls. PT participants were born at a gestational age (GA) < 33 weeks without CHD or severe developmental impairment. CHD individuals were term-born (> 36 weeks GA) and underwent open-heart surgery utilizing cardiopulmonary bypass during their first 2 years of life. Healthy control participants were age- and sex-matched recruited from the community. Participants underwent high-resolution T1-weighted magnetic resonance imaging (MRI) scans on a 3T scanner. Using 'Hippunfold', a validated automatic segmentation pipeline, volumes of the bilateral hippocampal subfields (i.e., Cornu ammonis CA 1-4, dentate gyrus, subiculum and Stratum Radiatum, Lacunosum, and Moleculare (SRLM)) were obtained. EF was assessed with the Behaviour Rating Inventory of Executive Function-Adult Version (BRIEF-A), a self-report questionnaire measuring EF in everyday life. Individual and clinical variables were systematically collected. Kruskal-Wallis test and Chi-Square test of independence were used to determine baseline differences between our groups. General linear models will be used to test group differences in hippocampal subfield volumes and their relationships to BRIEF-A scores.

Results High quality T1w images was available in PT, 55 CHD and 56 controls. Descriptive analyses to characterize the demographic and clinical features of our sample revealed that, as expected, three groups were comparable in age at MRI (mean age = 20 years) and sex. However, SES was significantly lower in both PT ($p<0.01$) and CHD ($p<0.001$) groups compared to healthy controls. Brain abnormalities on conventional MRI were more common in PT (26.8%) and CHD (23.6%) groups than in controls (12.5%), although this difference did not reach statistical significance ($p=0.055$). Hippocampal subfield volumes are currently extracted; subsequent volumetric analyses, adjusted for SES and total brain volume, will be completed by the end of July 2025. Associations between hippocampal volumes and EF scores remain to be examined.

Conclusions Early descriptive findings indicate significant SES differences between each clinical population and healthy controls, suggesting the need for SES adjustment in subsequent analysis. The next analytical phase will compare hippocampal subfield volumes across groups and examine whether these structural differences relate to executive function outcomes. These results will clarify whether hippocampal structure-function relationships differ across individuals with early-life adversities.

Program CHHD

PI Prof. Marie Brossard-Racine

10 - Integrating ctDNA and Clinical Parameters to Predict Treatment Response in HPV-Positive Head and Neck Cancer Patients

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Background Head and neck cancer (HNC) is the sixth most prevalent cancer worldwide, with an increasingly common subtype associated with HPV. Although HPV-positive HNC generally has a good prognosis, treatment varies depending on tumor severity and invasiveness, including surgery, radiotherapy, and systemic therapy. These treatments can cause lifelong complications and emotional distress, leading to high rates of depression and suicide post-treatment. Personalized strategies that minimize overtreatment are needed to reduce these adverse effects. Developing a predictive model to assess treatment response and minimal residual disease (MRD) using ctDNA alongside clinical and pathological factors could support more personalized decisions, improving patients' quality of life. Liquid biopsy, a minimally invasive technique, has proven effective in monitoring tumor status in cancers. By analyzing blood and saliva, tumor-derived DNA fragments can be quantified to help predict response. Therefore, evaluating treatment response and MRD risk is essential for guiding adjuvant therapy decisions.

Hypothesis The goal of this study is to develop a predictive model or set of criteria that integrates ctDNA levels, clinical factors, and pathological response to stratify patients by MRD risk and categorize them as non-responders, or as having minor, major, or complete responses to treatment to guide potential therapy de-escalation.

Methods The aim of this study is to develop a predictive model using ctDNA levels, imaging, tumor characteristics, and clinical/pathological factors to assess treatment response in HPV-HNC patients. We will analyze data from 100 patients at MUHC using an existing ctDNA and clinical databank. Liquid biopsy includes cfDNA extraction from blood and/or saliva (Qiagen EZ1/2 system), followed by ddPCR to quantify HPV-derived ctDNA with high sensitivity. Data such as age, gender, TNM stage, smoking history, radiologic response, and surgical margins will be collected. Statistical analyses (STATA 14.2) will evaluate associations with MRD and stratifying patients into non-, minor, major, or complete responders.

Results In assessing correlations between ctDNA levels, imaging data, clinical features, and pathological factors with treatment response and MRD risk in HNC, we expect to identify specific criteria and thresholds. For example, we predict that an elevated baseline ctDNA levels, larger tumor size, lymph node involvement, and clinical factors like smoking and alcohol use will be associated with higher MRD risk and an increased likelihood of minor or non-response to treatment. By identifying these correlations, we aim to develop a predictive model with different risk stratifications to estimate the likelihood of MRD post-treatment and assist physicians in determining the most appropriate management plan and when to change or de-escalate a treatment.

Conclusion Developing a predictive model to accurately assess the MRD risk as well as the rate of response of patients to treatment by including ctDNA and other clinical and pathological factors will be highly useful in guiding personalized treatment decisions, ultimately enhancing patients' quality of life.

Source of funding This research was supported by the McGill University Health Centre Foundation and the McGill Summer Research Bursary which supports medical students pursuing summer research in the Faculty of Medicine and Health Sciences.

Program CRP

PI Dr. Julia Burnier

14-36 - Development and Functional Testing of a Modular CRISPR Base Editing Platform for Hereditary Disease Research

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This project developed a modular CRISPR base editing platform to systematically investigate disease-driving mutations in hereditary disorders. Six backbone plasmids were constructed, combining three compact Cas variants (*CsIsrB*, *CwlIsrB*, *IscB*) with two base editors (*APOBEC*, *TadA*), each featuring a U6-driven sgRNA cassette for library cloning, Amp resistance, Puro selection, and Cre recombinase for conditional activation. Functional validation in mammalian cells confirmed the system's versatility for high-throughput screening.

The platform is being deployed to systematically screen coding and non-coding regions of WTp53, using pooled libraries of all six editor combinations. Parallel in vitro screens will identify proliferation-accelerating mutants, while in vivo studies—employing ultrasound-guided in utero delivery in PI3K-Notch HNSCC-prone models—will pinpoint tumour-driving variants. These screens will yield mechanistic insights into p53-driven tumorigenesis and functionally annotate clinically relevant p53 variants of uncertain significance (VUS). Beyond p53, the generalised platform enables scalable variant-to-function studies for diverse hereditary diseases, bridging molecular discovery with therapeutic insight.

As a CEGEP Year 1 student, this project provided hands-on training in molecular biology, mammalian cell culture, and functional genomics — equipping me with foundational skills for biomedical research while creating a versatile toolkit for hereditary disease studies.

Program CRP

PI Sampath Loganathan/ YiQing Lu"

3-15 - Assessing the Impact of Race on Machine Learning Models Predicting Hospital Admissions from Emergency Department

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Background: Although machine learning (ML) models are increasingly used as a tool to support clinical decision-making, concerns remain regarding their potential to perpetuate existing biases in the underlying data. As ML models function as an approximation of real-world decision-making, they provide a valuable tool to investigate how certain input variables and socioeconomic factors affect healthcare outcomes. This study aims to assess the impact of using race as a variable in predicting patient hospital admissions from the emergency department (ED).

Methods: We used the MIMIC-IV ED dataset (2011-2019), which comprises of 425,087 ED visits from patients at the Beth Israel Deaconess Medical Centre in Boston, Massachusetts. After preprocessing and excluding outlier or incomplete data, two multilayer perceptron models were trained - one with race as an input and one without. The predicted admission probabilities were compared across racial groups, and effect sizes calculated using Cohen's d. To control for noise, each model was initialized with the same weights, trained on identical batches, and evaluated over fifty runs with consistent training and validation sets

Results: The baseline model achieved an area under the curve of 0.842. Comparing models with and without race, including race led to significant differences in predicted admissions probabilities for White (3.2%), Black (-1.5%), and Hispanic (-3.0%) patients, all with large effect sizes (d=1.22, -0.65, -1.00 respectively), while no meaningful differences were observed for Asian (0.2%, d= 0.14) or Other (0.5%, d= 0.23) patients. These disparities persisted when racial groups were balanced but disappeared when race labels were randomized, confirming race-related prediction patterns. However, race is unlikely to be the only factor accounting for the observed differences in model predictions. Variation in insurance coverage across groups suggest that broader socioeconomic factors may also contribute to disparities attributed to race.

Conclusion: Our findings demonstrate that race influences ML predictions for hospital admission from the ED. These differences likely reflect systemic biases embedded in clinical practice and highlight the need for cautious use of race in algorithmic design. Future efforts should incorporate broader social determinants of health to support the development of more equitable ML tools.

Source of funding: This study is supported by the MUHC Foundation.

Program CRP

PI James Tsui

8-51 - Effects of Caldesmon Regulation on Smooth Muscle Actomyosin Interactions in the In Vitro Motility Assay

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INTRODUCTION

Smooth muscle (SM), found in most hollow organs like airways and vasculature, is critical to many physiological functions. SM contraction is driven by myosin molecular motors converting chemical energy (ATP) into mechanical work. This is primarily regulated by phosphorylation of the myosin regulatory light chain: myosin light chain kinase activates myosin, while myosin light chain phosphatase deactivates it. However, emerging evidence suggests that actin and myosin-binding proteins such as caldesmon (CaD) are also implicated in SM regulation. CaD has been shown to inhibit myosin ATPase activity and accelerate SM relaxation. However, its precise actomyosin modulatory mechanisms remain unclear, particularly during various phases of myosin activation.

OBJECTIVE AND METHODS

In this study, we used the in-vitro motility assay (IVMA) - a microscopy method enabling real-time visualization of fluorescently labelled actin filaments propelled by myosin motors - to examine CaD's modulation of actomyosin mechanics under varying myosin activation and density. Average actin filament velocity (Vavg), length, and the proportion of motile filaments were measured to assess CaD's regulatory effects.

RESULTS AND DISCUSSION

To test how CaD's effect varies with myosin activation, we measured Vavg at five myosin thiophosphorylation levels (0%-100%) in three conditions: 250nM CaD, 250nM bovine serum albumin (BSA) as a negative control, and no proteins added (0 CaD). As expected, Vavg decreased with reduced phosphorylation. Two-way ANOVA analysis showed no significant differences between Vavg in 0 CaD and BSA groups ($p > 0.3$ across all levels), validating BSA as a control. In contrast, CaD significantly reduced Vavg at all intermediate phosphorylation levels compared to 0 CaD ($p = 0.0004$ at 25%, 0.0001 at 50%, 0.0001 at 75%) and BSA groups ($p = 0.0001$ at 25%, 0.0021 at 50%, 0.001 at 75%). Vavg data normalized to mean Vavg at 100% myosin phosphorylation was fit to a nonlinear biophysical model describing Vavg as a function of myosin phosphorylation. With CaD the fitted curve was more linear (mean concavity = -0.42) and consistently lower than those of 0 CaD (mean concavity = -2.46) and BSA (mean concavity = -2.36), which overlapped significantly and showed sharper slope downwards at lower phosphorylations. Vavg decrease at lower myosin activations reflects fewer activated myosin heads propelling actin. Moreover, CaD's suppression of Vavg may reflect its hindering of myosin binding on actin filaments, effectively exacerbating the reduction of active myosins able to engage in motor interaction.

Vavg and filament length were then measured across thiophosphorylated myosin concentrations (10-150 ng/ μ L) with and without 250nM CaD. In both conditions, Vavg increased with length and fit an asymptotically saturating model: $V_{avg} = aV_{max}(1-(\theta L_0)/L)$, where aV_{max} represents maximal effective velocity and L_0 average inter-head spacing. Low Vavg at shorter lengths suggests that Vavg depends on the number of myosin-binding sites on filaments. aV_{max} with 250nM CaD was consistently lower than without, confirming CaD's role in hindering myosin binding to actin.

CONCLUSION

Our results suggest CaD's mechanism likely involves hindering myosin binding to actin. Overall, this advances the understanding of SM mechanics and may inform future strategies for addressing pathological SM dysregulation.

Program RESP

PI Anne-Marie Lauzon

9 - Changes in Pediatric RSV Hospitalizations after the COVID-19 Pandemic, 2022-2023, Canada: An Active Surveillance Study

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Background. The COVID-19 pandemic impacted RSV epidemiology. We describe Canadian pediatric tertiary care RSV hospitalizations in 2022-2023 and assess pandemic-related changes.

Methods. Active surveillance of hospitalized children aged 0-16 years was conducted at 13 Immunization Monitoring Program, Active (IMPACT) centres. RSV hospitalizations in 2022-2023 were compared to those in the pre-pandemic period (2017-2018 through 2019-2020). Province-specific and age-stratified proportions of all-cause hospitalizations with RSV detection and age-stratified proportions of RSV-associated intensive care unit (ICU) admission were calculated. Changes in seasonality were described using epidemic curves and Seasonal Autoregressive Integrated Moving Average (SARIMA) modelling.

Results. In 2022-2023, there were 5872 RSV-associated hospitalizations including 1260 (23.5%) ICU admissions, both more than double pre-pandemic yearly averages. Overall, median (IQR) age increased from 6 months (1-20) to 9 months (2-27; $P < 0.001$). The proportion of RSV-associated hospitalizations among all-cause hospitalizations increased by 3.5 percentage points (95% CI 3.3-3.7), to 7.0%. While 41.5% of hospitalizations were among children <6 months old, they accounted for 62% of ICU admissions. Overall, ICU proportion remained constant; however, odds of ICU admission among infants <6 months old increased (adjusted OR 1.35, 95% CI 1.2-1.52) compared to the pre-pandemic period. National weekly incidence in 2022-2023 peaked earlier, higher and persisted longer than expected by SARIMA.

Conclusions. In 2022-2023, the number of RSV hospitalizations and ICU admissions increased dramatically in Canadian pediatric hospitals. Despite an older age distribution, the greatest burden remained in children <6 months old. RSV immunization strategies for young infants will likely have substantial potential public health impact.

Source of Funding: IMPACT RSV surveillance was managed by the Canadian Paediatric Society and funded by the Public Health Agency of Canada's Centre for Immunization and Respiratory Infectious Diseases; student stipend supplemented by Mitacs Accelerate.

Program IDIGH

PI Dr. Jesse Papenburg

8-52 - NMDA receptors determine spine density of cortical layer-5 pyramidal cells

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¹BRaIN

Introduction: N-methyl-D-aspartate receptors (NMDARs) are a major type of glutamate receptors ubiquitously expressed at synapses across the nervous system. Classically known as coincidence detectors, NMDARs play a crucial role in Hebbian plasticity and memory formation due to their ability to sense simultaneous pre- and postsynaptic activity. Moreover, NMDARs have been shown to maintain spine stability and maturation, however, the contribution of these receptors in shaping inter- or intracortical connectivity remains poorly understood. To address this gap, we investigated the impact of global and sparse genetic NMDARs deletion on dendritic spine density in layer-5 pyramidal cells (L5 PCs) of mouse primary visual cortex (V1). As V1 L5 PCs mainly communicate with each other via their basal tertiary branches, we hypothesized that NMDAR removal would reduce spine density here.

Materials and Methods: Global deletion NMDARs was achieved using an $Emx1^{cre/+}; NR1^{flox/flox}; Ai9^{tdtomato/+}$ triple transgenic mouse model that excised the gene encoding for the obligatory GluN1 subunit on a global scale, while sparse deletion was introduced via local injection of AAV-eSYN-mCherry-iCre virus into neonatal $NR1^{flox/flox}$ mice to conditionally remove (KO) GluN1 in V1 L5 PCs. Biocytin-loaded patch-clamped PCs were stained with fluorescent dye-conjugated streptavidin and 3D confocal image stacks were acquire. Spines were manually counted, and statistics were conducted in Igor Pro 9.

Results: Global NMDAR deletion reduced overall spine density in KO PCs compared to control PCs obtained from WT littermates (KO: 0.27 ± 0.02 spines/m, $n = 60$ vs. WT: 0.37 ± 0.02 spines/m, $n = 65$, $p < 0.001$). KO PCs also exhibited lower spine density specifically at secondary branches (KO: 0.27 ± 0.02 spines/m, $n = 19$ vs. WT: 0.42 ± 0.03 spines/m, $n = 20$, $p < 0.001$), and tertiary branches (KO: 0.29 ± 0.03 spines/m, $n = 24$ vs. WT: 0.41 ± 0.03 spines/m, $n = 4$, $p < 0.01$). In contrast, sparse NMDAR deletion only reduced spine density on tertiary branches in KO PCs (KO: 0.49 ± 0.02 spines/m, $n = 104$) compared to WT PCs within the same slice and control PCs from animals injected with saline only (pooled: 0.58 ± 0.03 spines/m, $n = 99$, $p < 0.05$). Interestingly, we did not observe any differences in overall spine density following sparse NMDAR removal (KO: 0.48 ± 0.02 spines/m, $n = 174$ vs. WT: 0.52 ± 0.02 spines/m, $n = 230$, $p = 0.12$), however, KO PCs displayed lower spine density at distal dendrites located beyond $60 \mu m$ from the soma (KO: 0.56 ± 0.03 spines/m, $n = 83$ vs. WT: 0.63 ± 0.02 spines/m, $n = 131$, $p < 0.05$).

Conclusion: In summary, my findings indicate that NMDARs are a key regulator of neocortical connectivity and structural plasticity. Furthermore, the difference in overall spine density between global and sparse deletion suggests that this regulatory function operates in both a cell-autonomous and circuit-wide manner. Since NMDARs have been implicated in major neuropathologies such as Alzheimer's, autism, and epilepsy, my observations will greatly benefit the development of novel and improved therapeutic strategies in these areas.

Program BRaIN

PI Dr. Jesper Sjöström

7-44 - Meta-analysis of scRNA-seq and snRNA-seq reveals differences in transcriptomic heterogeneity between hiPSC-CMs and hiPSC-CM derived organoids, when compared to tissue isolated CMs from healthy and cardiomyopathy patients

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Introduction: In Canada, heart failure (HF) is an alarming cause of cardiovascular mortality. Approximately 2.26% of the Canadian population or 850,000 individuals suffer from HF. Unfortunately, heart transplantation remains the only treatment option to reverse chronic damage caused by HF. Recent advances in personalized medicine have identified human induced pluripotent stem cells (hiPSCs) as a potential treatment for HF. hiPSCs may differentiate into cardiomyocytes, paving the way for eventual transplantation into patients with end-stage HF. Due to extensive cardiomyocyte heterogeneity in HF patients, transplantation of hiPSC-derived cardiomyocytes (hiPSC-CMs) will likely need to be personally tailored to each HF patient. However, the HF cardiac microenvironment has not been extensively elucidated in the literature. The investigation of cardiomyocyte heterogeneity also revealed that more functional hiPSC-CMs (as assessed by contractile function, gene, and protein expression) are required. Here, we aim to characterize the HF cardiac microenvironment *in silico* and elucidate transcriptomic differences between different types of cardiomyocytes.

Material and Methods: We performed a meta-analysis on publicly available single-cell and nuclei datasets containing transcriptomic information on hiPSC-CMs, hiPSC-CM derived organoids, and different modes of HF. 8 independent experiments were analyzed. Expression matrices containing gene counts in each sample were matched with their corresponding metadata and analysis was performed following Seurat 5.1.0. A negative binomial linear model was created to analyze differentially expressed genes across different iPSC-CM and HF conditions to elucidate cell-type and condition-specific changes.

Results: 16 heterogeneous cardiomyocyte populations were revealed based on transcriptomically distinct signatures after dataset integration of hiPSC-CMs, hiPSC-CM derived organoids, and different modes of HF using canonical correlation analysis. Indeed, immature hiPSC-CMs primarily contained PTMA+ cardiomyocytes, indicating an embryonic-like, proliferative state when compared to mature adult human cardiomyocytes. Interestingly, these cells resemble that of hiPSC-CM derived organoids in terms of cell-type abundance proportions and transcriptomic expression based on SCT-normalized data. hiPSC-CMs and hiPSC-CM derived organoids also express a distinct type of cardiomyocyte that have transcriptomic signatures belonging to both fibroblasts and smooth muscle cells. Finally, cell type and transcriptomic similarity indexes demonstrate that hiPSC-CMs have a minor degree of similarity when comparing to cardiomyocytes from ischemic cardiomyopathy.

Conclusions: In this meta-analysis, we present the existence of distinct, heterogeneous cell types within hiPSC-CMs, hiPSC-CM derived organoids, and HF populations. We show that laboratory-grown cardiomyocytes remain embryonic in phenotype and exhibit cardiomyocyte populations that are transcriptomically distinct from healthy adult cardiomyocytes. We intend on using these findings to compare them to our patient population here in the Heart-in-a-Dish project. Ultimately, we hope our research can improve the functionality and maturity of hiPSC-CMs within the *in vitro* differentiation process.

Source of Funding: The Cecere lab is supported by the Trottier Family Foundation, the Heart-in-a-Dish project, and the Courtois Cardiovascular Signature Program. BL (The principal author) is supported by the 2024/2025 Canada Graduate Scholarships - Master's Program (CIHR), the 2025 RI-MUHC Studentship, and the 2025/2026 Santé Sector - Master's Training Scholarships - BF1 from the Fonds de recherche du Québec (<https://doi.org/10.69777/368528>).

Program SIS

PI Renzo Cecere

14-37 - 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: NSERC USRA, RI-MUHC

Program BRaIN

PI Dr. Wei-Hsiang Huang

1-06 - Evaluating Toolkits for Inclusion, Diversity, Equity and Accessibility in Clinical Trials: A Scoping Review

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Background:

While numerous toolkits have been developed worldwide to guide researchers in designing and conducting inclusive clinical trials, their relevance and usability within Canada's diverse population remain uncertain. This scoping review aimed to examine existing toolkits and evaluate their suitability for supporting inclusive clinical research in the Canadian context.

Methods:

We conducted a comprehensive search of peer-reviewed and grey literature from April to May 2025 across multiple databases, including MEDLINE, EMBASE, CINAHL, PsycINFO, Cochrane, Scopus, and Web of Science. Search terms combined concepts related to equity, diversity, and inclusion with toolkits and clinical trials. Two independent reviewers screened the articles based on predefined inclusion and exclusion criteria. Data was extracted using a standardized form focused on toolkit content, and findings were summarized in a matrix and tabular format for comparison.

Results:

Out of 4,247 records screened, 158 articles met the inclusion criteria. Most toolkits addressed strategies for enhancing Inclusion, Diversity, Equity, and Accessibility (IDEA), with a strong focus on targeted recruitment approaches. Common strategies included building long-term, trust-based partnerships with communities; co-designing trials with diverse populations; using inclusive site selection; and broadening eligibility criteria. Toolkits also emphasized the importance of accessible recruitment materials—such as multilingual, plain-language resources and digital tools—alongside participant supports like transportation, fair compensation, and multicultural staff. Monitoring frameworks were frequently proposed, including real-time demographic tracking, enrollment targets, and diversity dashboards to ensure accountability. These findings informed the development of a user-friendly toolkit adapted to the Canadian clinical research environment.

Conclusion:

While global toolkits offer valuable guidance, most were not developed with the Canadian sociocultural and healthcare context in mind. There is a clear need for further work to co-create a toolkit tailored specifically to Canada's diverse populations, in partnership with underrepresented communities. Future efforts should prioritize a Canada-specific approach grounded in equity, cultural relevance, and accessibility to support inclusive clinical trials nationwide.

Ethics and dissemination: The protocol was registered on the Open Science Framework

<https://doi.org/10.17605/OSF.IO/UDQBJ>

Program CHAL

PI Louise Pilote

13-30 - Response to Modafinil in People with Mitochondrial Disorders: A Retrospective Case Series

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Background: Modafinil is a psychostimulant that is approved for treatment of certain sleep disorders, including narcolepsy, obstructive sleep apnea, and shift work sleep disorder. However, modafinil may have broader applications, and has been used off-label in a range of other conditions. In this retrospective study, we investigated the therapeutic potential of modafinil for people with mitochondrial disorders.

Methods: We reviewed our clinical and research databases to identify patients diagnosed with mitochondrial disorders who had been treated with modafinil for any reason. We then conducted a thorough chart review for each patient meeting inclusion criteria, and extracted relevant clinical data, including the following: demographics, clinical phenotype, genetic diagnosis, indication for modafinil, modafinil dose, duration of treatment, clinical response, and reported side effects.

Results: We identified four patients that met the inclusion criteria. The effects of the treatment for these patients were overall beneficial. Two patients reported improved energy, improved sleep, and improved cognitive function. One patient experienced no significant benefit. Some adverse effects were experienced with one patient, such as dry mouth, anxiety, and difficulty with sleep maintenance.

Conclusions: Modafinil may benefit patients with mitochondrial disorders by reducing fatigue and improving cognitive function. However, larger studies are necessary to confirm these findings.

Program CHHD

PI Dr. Kenneth Myers

15-45 - Characterizing the role of IQGAP1 as a novel interactor of Trio in axon outgrowth and guidance

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Introduction

During brain development and the formation of neuron circuits, neurons extend their axons toward specific synaptic targets in response to extracellular guidance cues. Small Rho GTPases are essential regulators of cytoskeletal dynamics and have been shown to be critical for axon outgrowth and guidance. The localized recruitment and activation of these GTPases depend on numerous GTPase-activating proteins (GAPs) and guanine nucleotide exchange factors (GEFs). Trio, as a GEF, activates both Rac1 and RhoA through its GEF domain, and is a key mediator between extracellular guidance cues and cytoskeletal dynamics. Previous studies have shown that Trio deficiency leads to defects in axon outgrowth and guidance.

To identify the global Trio interactome and determine additional proteins potentially involved in axon outgrowth, proximity-dependent biotin identification (BioID) assay was used, which tagged nearby proteins in living cells. The Trio interactome revealed key candidates associated with Rho GTPases and neuronal development, such as IQGAP1—a scaffolding protein that stabilizes the active, GTP-bound form of Rac1 and regulates cell migration and polarization. We hypothesize that IQGAP1 interaction with Trio regulates Rac1 activity in the signaling pathways involved in axon outgrowth and guidance.

Methods

To investigate the IQGAP1-Trio colocalization, immunofluorescence staining will be performed in N1E-115 neuroblastoma cells and dissociated rat cortical neurons using IQGAP1 and Trio antibodies. To evaluate the potential interaction of IQGAP1 with Trio, HEK293 and N1E-115 cells will be co-transfected with GFP-tagged IQGAP1 and Trio constructs, followed by co-immunoprecipitation. To test whether this interaction occurs under endogenous conditions, co-immunoprecipitation assays will be conducted in dissociated rat cortical neurons using IQGAP1 and Trio antibodies. To map the interacting domains of Trio with IQGAP1, HEK293 cells will be transfected with various Trio deletion constructs, and co-immunoprecipitation will be used to assess interaction with IQGAP1.

Result

Western blot analysis confirmed that the IQGAP1 antibody detects the endogenous protein in both HEK293 and N1E-115 cells, validating its use for further experiments. Based on these findings, endogenous IQGAP1-Trio interaction will be examined through co-immunoprecipitation in dissociated cortical neurons. Immunofluorescence microscopy revealed that endogenous IQGAP1 is localized to the plasma membrane and cell-cell contacts in N1E-115 neuroblastoma cells. Additional immunostaining in dissociated rat cortical neurons is planned to determine the colocalization of IQGAP1 and Trio.

Conclusion

This study aims to define the role of IQGAP1 and how its interaction with Trio affects cytoskeletal dynamics, neurite extension during neuronal development, making IQGAP1 protein a potential target for studying neurodevelopmental diseases.

Program CRP

PI Nathalie Lamarche-Vane

13-31 - AI-Driven Personalized Exercise Planning for People Living with HIV: An Intervention to Improve Physical Activity and Health Outcomes through the MARVIN Chatbot

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Background: As people living with HIV (PLWH) live longer, managing their physical and mental health is vital. Although exercise offers clear benefits for PLWH, only 51% meet Canada's recommended 150 minutes of weekly moderate activity, less than the general population. Barriers to exercise include uncertainty about starting/maintaining exercise, and limited access to physiotherapists/trainers, often not covered by provincial health insurance. Physicians also face time and training constraints in offering exercise guidance. The use of an AI-based chatbot, MARVIN, developed by our research team, could be a cost-effective solution via integration of a module with a decision tree-based algorithm to translate patient conversations into personalized exercise plans. We hypothesize that personalized fitness plans generated through chatbot communication will lead to greater exercise duration and intensity, better adherence, and improvements in secondary outcomes such as mental health, energy levels, and social engagement areas in which PLWH often face challenges compared to the general population.

Methods: To build the decision tree, the principal questions were developed based on literature in exercise programming, prompt engineering strategies, and expertise in exercise planning. These questions assess activity level, injury risk, and exercise preference through a chatbot dialogue, generating tailored 8-week plans that match participant ability and goals. An 8-week exercise plan duration was selected based on existing literature, as it allows sufficient time to establish habits while reducing the influence of initial novelty. Exercises were selected for improving cardiovascular health and/or strength, with some adapted from the already validated TEMPO platform for prostate cancer patients. The module's effectiveness will be tested in a pilot trial against a generic exercise plan, with participants recruited from CVIS (HIV Unit at MUHC). Assessments will occur at baseline, 4 weeks, 8 weeks (end of intervention), and 3 months post-intervention to evaluate adherence and short-term impact. Primary outcomes include changes in exercise frequency, duration, and intensity; secondary outcomes include mood, energy, and motivation. Data will be analyzed using statistical tests, frequency tables, and visual figures to assess the intervention's effectiveness.

Results (module development): A decision tree with six principal questions leading to 97 discrete endpoints was developed to guide exercise planning. Each endpoint corresponds to either an 8-week personalized exercise program or curated resources for group-based fitness, depending on user preference. This decision tree was integrated into the MARVIN chatbot allowing a back and forth conversation to answer the questions necessary to provide the personalized exercise plan. The pilot trial described will be developed to assess the effectiveness of the module.

Conclusion: MARVIN has the potential to become an AI-driven personalized coach for PLWH without increased strain on the healthcare system. The early development of the module has already provided valuable insights, and the upcoming pilot trial is expected to further evaluate the chatbot's potential in delivering personalized exercise programming to increase exercise frequency and improve secondary outcomes among patients with chronic illnesses.

Source of funding This study was supported by the McGill Centre for Viral Diseases (MCVD) and D2R through the MCVD Summer Undergraduate Research Fellowship.

Program IDIGH

PI Dr. Bertrand Lebouche

1-07 - A Decision-Support Algorithm for Optimizing Perinatal Transfers in Quebec: Integrating Objective Data and Occupancy Metrics

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Introduction:

Quebec's tertiary neonatal intensive care units (NICUs) admit approximately 4,200 neonates annually, many of whom require inter-hospital transfers for specialized care. Currently, perinatal transport (maternal and neonatal) is coordinated by a centralized provincial transport center (CCPPQ), which relies heavily on subjective assessments of NICU bed availability and staffing. This approach lacks consistent, objective criteria, limiting its efficiency and potentially contributing to delays in care and patient safety risks. The objective of this study is to develop a decision-support algorithm (DSA) based on objective criteria and to evaluate its potential impact on admission decisions, operational efficiency, and patient safety.

Methods:

Two Delphi rounds (March-October 2024) involving 17 stakeholders from all six NICUs and the CCPPQ were conducted to identify and prioritize key factors influencing transfer decisions and to map out the decision-making process. These findings were synthesized into a DSA.

The DSA was then applied in an AI simulation using historical neonatal transport cases (2021-2023) to evaluate its performance. In parallel, an occupancy rate alert sheet was developed, leveraging data from Quebec's existing provincial occupancy platform (Sit-Neo) as well as an adapted local version from one participating NICU. Extensive stakeholder engagement through focus groups and individualized sessions ensured that the tool accurately reflected each NICU's operational realities, creating standardized and broadly applicable criteria.

Results:

The Delphi process confirmed care type (100% agreement) and NICU occupancy (>82% agreement) as top priorities, with distance and nurse-to-patient ratios also highly rated. Critical factors identified for determining the optimal admitting unit included (a) the type of patient care required and (b) a harmonized, evidence-based, unit-level color code for capacity to admit, calculated using occupancy, real-time nursing resources, and planned unit turnover.

The newly developed occupancy alert sheet categorizes NICU status as green (open), yellow (near saturation), or red (saturated). An AI simulation applying the finalized DSA to 1,490 historical neonatal transport cases indicated that approximately 30% of transfers could have been optimized toward NICUs with lower occupancy.

Discussion:

Integrating standardized, objective occupancy data into transfer coordination processes addresses previously underrecognized operational challenges, improves transparency, and establishes a universal communication framework across Quebec's NICUs. This combination of stakeholder-driven prioritization and pragmatic operational tools demonstrates substantial potential for improving neonatal transport efficiency and patient outcomes.

Conclusion:

The DSA and real-time NICU occupancy alert sheet aim to deliver a standardized, data-driven approach for perinatal transfer coordination. Future work will assess their real-world implementation and impact on patient safety, transfer outcomes, and the optimization of NICU resources province-wide.

Program CHHD

PI Dr. Marc Beltempo

4-27 - Mapping Stress-Induced Activation in the Cerebellum

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The cerebellum's role in coordinating and refining motor activity is well-established; recent studies have also demonstrated its involvement in emotion and stress-related behaviour. Furthermore, the cerebellum is known to form functional circuits with the limbic system—a critical network orchestrating the stress response—and it expresses the receptors required to process the neurochemical mediators of the stress response. However, the specific areas and cell populations activated in response to stress have not yet been mapped. Therefore, this project uses the protein c-Fos, an immediate early gene product, to provide this essential map, guiding further research on the stress-related circuits in the cerebellum.

Wild-type mice aged p35-p55 were randomly assigned to one of three experimental groups: acute immobilization stress (AIS), where the mice were completely immobilized for 2h; handled controls (HCTL), where the mice were exposed to the same conditions as the AIS mice, but without immobilization; and naïve controls (CTL), which were left undisturbed in the home cage. After the mice underwent their respective behavioural protocols, their cerebella were extracted, immunostained for c-Fos, and imaged using an epifluorescent microscope to analyze stress-induced patterns of activation in the granule cell layer (GCL) and molecular layer (ML) of the vermis and hemispheres.

Preliminary results looking at the granule cell layer suggest a pronounced increase in c-Fos expression in crus I, a region implicated in the stress response in mice and humans, in the AIS group compared to the CTL group. Additionally, the HCTL group appears to show an increase in c-Fos expression throughout most regions in the vermis compared to the CTL group, suggesting that a component outside of the immobilization stress itself is sufficient to induce c-Fos expression in mice. Interestingly, this increased activation was not observed in the vermis of the AIS group as compared to the CTL group, suggesting that acute immobilization stress may override or modulate the HCTL activation in the vermis. Importantly, the CTL group exhibited little to no activation in any of the imaged regions, supporting that the increased c-Fos expression observed in the AIS and HCTL groups was reflective of experience-dependent activation and not baseline activity. These findings are preliminary and will continue to be investigated in future cohorts and further analysis of the data.

Mapping stress-induced activation of the cerebellum provides the critical link between brain and behaviour, allowing for targeted study of the cerebellum's role in mental health and neurodevelopmental disorders, as well as enhancing current models of emotion and cognition. Our lab recently discovered that stress impacts cellular function in the mouse cerebellum, measured as a change in the firing properties of the output neurons of the cerebellar cortex, the Purkinje cells. This research will guide these experiments, targeting the specific regions that are active during acute stress.

This project is supported by the McGill Faculty of Medicine and Health Sciences NSERC Undergraduate Student Research Award and the Suvrathan lab.

Program BRaIN

PI Aparna Suvrathan

2-10 - The Association between Hypertension and Accelerated Brain Aging: The Role of Gender-Related Factors

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Introduction: Hypertension is the leading global risk factor for mortality and a major contributor to vascular diseases such as stroke and heart disease, yet its prevalence continues to rise despite being preventable. Early onset hypertension may negatively affect brain health over time. Brain age, often estimated through neuroimaging such as MRI or cognitive metrics, reflects the biological aging of the brain, with the brain age gap (BAG) representing the difference between predicted and chronological age. Both biological sex and gender-related factors, such as education, socioeconomic status, and occupational roles, appear to influence brain health, though the association between gender-related factors and the relationship between hypertension and brain aging remains poorly understood. This study aims to examine whether gender-related factors impact the association between hypertension and BAG using UK Biobank neuroimaging data.

Methods: We included participants from the UK Biobank, a large population-based cohort of 502,505 participants aged 40-69 at baseline assessment (2006-2010), collected across 22 assessment centres in the United Kingdom. We focused on participants with MRI data that was collected at 2014 follow-up, to estimate brain age. BAG was calculated as predicted brain age minus chronological age and corrected for age-related bias. To reduce confounding, we applied propensity score matching (1:1 hypertensive:normotensive) and separated the participants into five categories based on age of hypertension diagnosis (<35, 35-44, 45-54, 55-64, ≥65 years). Multivariable linear regression assessed the association between hypertension and BAG, adjusting for key covariates. Twenty-one gender-related factors, categorized into 3 dimensions (social, psychological, and neighbourhood factors), were explored.

Results: A total of 20,268 participants with complete neuroimaging data were analyzed (mean age: 57 years, 53% males). Compared to normotensive controls, participants with hypertension had a greater prevalence of certain gender-related factors, notably living alone, emotional distress, low annual household income, and health deprivation. After adjusting for covariates, hypertensive participants exhibited a significant 0.57-year increase in brain age gap compared to normotensive controls (95% CI: 0.44-0.69, $p < 0.0001$), demonstrating premature cerebrovascular structural changes. Of the gender-related factors, participants who reported living alone with hypertensive exhibited a significant increase in brain age gap (0.21, 95% CI: 0.05-0.37, $p = 0.0119$), compared to participants without hypertension.

Conclusions: These findings indicate that hypertension is associated with an increased brain age gap, even after adjusting for covariates. Living alone significantly contributed to accelerated brain aging. These results underscore the importance of addressing vascular risk factors in midlife and taking into account social determinants to promote healthy brain aging.

Source of Funding: This project was supported by the Dr. Clarke K. McLeod Memorial Scholarship awarded to the author, which provided funding for their research involvement.

Program CHAL

PI Louise Pilote

5-32 - The utility of interferon-gamma release assays in the context of a positive tuberculin skin test: a systematic review and meta-analysis

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Introduction: The treatment of tuberculosis infection is guided by diagnostic tests: the tuberculin skin test (TST) and/or interferon-gamma release assay (IGRA). While the TST is much more widely available for diagnosis, its specificity is lower than the IGRA. Therefore, confirmatory IGRA tests among people who are TST-positive are often performed prior to prescribing treatment. Yet, the added value (and potential risks) of using a confirmatory IGRA to guide treatment have not been assessed. Therefore, we conducted a systematic review and meta-analysis to estimate the benefits and consequences of using an IGRA after a positive TST to guide treatment of tuberculosis infection.

Methods: We searched MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials for articles published between 1 January 1990 and 5 May 2025. Two reviewers independently screened all studies for eligibility and assessed quality using an adapted quality assessment tool for observational studies (QUADAS-2). One reviewer performed data extraction into a standardized Excel spreadsheet. Eligible studies included retrospective or prospective cohort studies and randomized trials with ≥ 10 untreated participants who tested TST-positive, had an IGRA performed (QuantiFERON/T-SPOT.TB), and were followed for ≥ 12 months. Studies of treated individuals, TST converters or boosters, vaccinated populations (e.g., BCG), or those without IGRA testing were excluded. Our primary outcome was the incidence rate ratio (IRR) of TB disease between participants who were TST-positive, as compared to those who were either TST-positive, IGRA-negative or TST-positive, IGRA-positive. Secondary outcomes included the difference in the proportion of people treated when a confirmatory IGRA was used and rates of TB disease per 1000 person-years by test outcome. Data were pooled using random effects generalised linear mixed models and heterogeneity estimated with I^2 .

Results: We identified 7396 total studies and included 18 in our review. Preliminary results suggest that among 12 studies evaluating the QuantiFERON IGRA and TST at a positive cut-point of ≥ 10 mm, the IRR for TB to be 2.28 (95% CI: 1.38-3.77; $I^2 = 73.8\%$) for those IGRA-positive and TST-positive and 0.52 (95% CI: 0.36-0.74; $I^2 = 10.5\%$). Use of a confirmatory IGRA to guide treatment of TB infection reduced the number of people treated by 71% (95% CI: 49-86%; $I^2 = 98.9\%$), however the risk of TB disease per 1000 person years among people TST-positive and IGRA-negative was 1.2 (95% CI: 0.3-4.8; $I^2 = 90.0\%$). Findings were qualitatively similar among 3 studies evaluating T-SPOT.TB IGRA.

Conclusions: The risk of TB disease is substantially higher in people who are both TST- and IGRA-positive, and confirmatory testing can substantially reduce the number of people treated, but people TST-positive and IGRA-negative still are at risk for TB disease and could benefit from treatment.

Source of funding: This research project is supported by the Respiratory Epidemiology and Clinical Research Unit (RECRU) Summer Studentship Award awarded to Raphaëlle Noseworthy and by a Canadian Institute of Health Research (CIHR) grant awarded to Dr Dick Menzies.

Program RESP

PI Jonathon Campbell, Dick Menzies

9-06 - Variants Validating a zebrafish model for PCD variant interpretation using a known loss-of-function DNAAF1 variant

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Introduction: Primary Ciliary Dyskinesia (PCD) is a rare, autosomal recessive disorder caused by mutations in genes essential for motile cilia function, including *DNAH5*, *DNAAF1*, and *HYDIN*. Disruption of motile cilia impairs mucociliary clearance and left-right body axis patterning, leading to chronic respiratory disease and situs abnormalities. While genetic testing offers a comprehensive diagnostic tool, its impact is often limited by the high rate of variants of uncertain significance (VUS). Zebrafish represent a robust in vivo model for functional variant assessment of VUS in PCD genes. Morpholino knockdown of *dnaaf1* in zebrafish produces observable phenotypes such as hydrocephaly and laterality defects. Co-injection of morpholino with wild-type or variant human mRNA allows for phenotypic rescue analysis. Successful rescue suggests the variant is benign, while failure suggests pathogenicity. Prior work in our lab demonstrated that the *DNAAF1* N255K variant, a VUS and found in a patient was able to rescue both hydrocephalus and laterality defects in zebrafish with *dnaaf1* knockdown, making it an example of how functional testing can resolve uncertain clinical variants. However, to validate the assay's interpretive value, it is essential to include known loss-of-function (LoF) variants that serve as negative controls. Here, I aimed to generate and test the *DNAAF1* Y264* nonsense variant, which is predicted to result in a truncated, nonfunctional protein. Establishing that Y264* fails to rescue the zebrafish phenotype would confirm its role as a reliable LoF control and validate the dynamic range of the rescue assay for future VUS testing.

Methods: We designed primers to introduce the Y264* variant into a human *DNAAF1* expression construct using site-directed mutagenesis. PCR was performed with Q5 Hot Start High-Fidelity polymerase, followed by Kinase-Ligase-DpnI (KLD) treatment. The product was transformed into *E. coli*, and plasmids were extracted via miniprep. Sanger sequencing was used to confirm the presence of the mutation. For functional testing, zebrafish embryos were injected at the one-cell stage with morpholino to knock down *dnaaf1*, along with either wild-type or variant human *DNAAF1* mRNA, and then screened for rescue of laterality defects and hydrocephaly.

Results: The PCR initially failed due to poor primer binding at higher temperatures, but lowering the annealing temperature led to clear bands. *DpnI* digestion and transformation into *E. coli* were successful. However, Sanger sequencing revealed that the Y264* mutation was not present, indicating unsuccessful mutagenesis despite clean PCR and transformation. In contrast, the N255K missense variant, previously tested in our lab, showed complete phenotypic rescue, supporting its reclassification as likely benign.

Conclusions: The *DNAAF1* N255K variant was functionally validated in zebrafish, demonstrating the utility of zebrafish as a rapid in vivo model for reclassifying VUS in PCD genes. The Y264* variant remains a critical negative control for validating zebrafish-based functional assays of PCD-associated variants. Although initial mutagenesis attempts failed, establishing this control remains a key objective for our lab. Its inclusion will ensure the assay's ability to discriminate between functional and non-functional variants, thereby enabling more confident reclassification of VUS for individuals with suspected PCD.

Source of Funding: Le Grand Défi Pierre Lavoie Fondation

Program CHHD

PI Thomas Kitzler

3-20 - Development of a Pipeline for CHAMP, a Chatbot to Support Clinical Decision-Making in Pediatric Care

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Background:

Each year, nearly two million children and youth visit Canadian Emergency Departments (EDs), often for concerns that could be managed with timely and reliable information. While AI chatbots offer a promising solution, large language models (LLMs) are prone to generating inaccurate or hallucinated responses which is a serious limitation in medical contexts. To address this, our team is co-constructing CHAMP, a Chatbot to Assist the Management of Paediatric patients. This project focuses on designing a knowledge database pipeline that enables CHAMP to retrieve accurate health information from validated documents and generate high-quality, trustworthy responses.

Methods:

The project consists of a knowledge database pipeline with multiples steps. First, we converted each validated document into plain text and split it into hierarchical “chunks”. We used “Heading 1” boundaries for broad sections and then subdivided long paragraphs into smaller units to keep each chunk focused. Second, we encoded each chunk into a semantic vector (using a transformer-based embedding model) and indexed all vectors with FAISS (Facebook AI Similarity Search) to enable sub-second retrieval. At query time, the user's question is embedded and matched to the most relevant chunks, which are returned exactly as the chatbot's response.

To evaluate answer quality, we created a set of three test questions along with reference answers derived directly from the original validated documents. Responses were assessed a healthcare pediatric professional based on two criteria: 1) conciseness (50 word target) and 2) completeness (contains essential medical recommendations).

Results:

We processed five validated pediatric health documents and divided them into 143 smaller sections (approximately 27 per document). The preparation and indexing steps took around 15 seconds. When a user submits a question, the system retrieves relevant information in about 19 seconds on average.

Three clinically relevant pediatric questions, aligned with the content of the validated source documents, were tested and their responses rated: 1) overall concise except one overly long answer. The model included more detailed explanations than necessary, leading to verbose outputs. 2) Although those answers were factually accurate and relevant, they lacked actionable advice, such as where to seek medical help.

Conclusion:

This project lays the foundation for a health chatbot system that can provide pediatricians and the general public with timely, accurate, and relevant health information. By building a pipeline that extracts trusted health content from validated documents and matches it to user questions, the system aims to improve access to reliable guidance to the users' questions.

Program IDIGH

PI Esli Osmanliu

11-19 - Atrolnc-1 as a Key Modulator of NFkB Signaling in Muscle Autophagy and Inflammatory Responses

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Background:

Long non-coding RNAs (lncRNAs) are defined as >200 nucleotides RNAs that lack protein-coding potential. lncRNAs have emerged as crucial regulators of gene expression as they are involved in various cellular processes including autophagy and muscle regeneration. Atrolnc-1 (Atrophy-related long noncoding RNA-1 (1110038B12Rik)) has been identified as possible regulator of NFkB transcription factor in skeletal muscles. The role of Atrolnc-1 in the regulation of proteolysis and cytokine production in skeletal muscles remains unknown. Our study aims to elucidate functional significance of Atrolnc-1 in autophagy regulation using a targeted knockdown (KD) approach in a murine model.

Methods:

16-weeks old mice were injected intramuscularly with adeno-associated virus (AAV) vectors encoding Atrolnc-1 shRNA (KD) in one leg or a scrambled control (scrmb) in the contralateral leg into the gastrocnemius (GAS) muscles to induce localized Atrolnc-1 KD for 6 weeks. In an additional group of animals, we stimulated toll-like receptors using i.p. injection of *E. coli* lipopolysaccharide (LPS) for a period of 24 hours in the whole animal. Muscles were harvested, and a gene expression and fibre type distribution were measured using qPCR and immunofluorescence (IF) staining.

Results:

Successful Atrolnc-1 KD was confirmed using qPCR, evidenced by a significant decrease in Atrolnc-1 mRNA expression without any change in muscle weight. Atrolnc-1 KD significantly increased basal expression of several autophagy-related gene (Lc3b, Gabarapl1, Sqstm1, ULK1, Beclin1, Atg5, Bnip3, Cathepsin L) after 6 weeks confirming its role in the regulation of muscle autophagy. Additionally, significant increase in the basal levels of the ubiquitin E3 ligases gene expression (Atrogin-1, Murf-1, Musa1) and proteasome subunits (B5, B8, B9, B10) was also observed suggesting the involvement of Atrolnc-1 in muscle atrophy and mass maintenance. Inflammatory cytokines like IL-6 and Fn14 showed a significant increase in basal gene expression following 6 weeks of Atrolnc-1 KD which further supports the involvement of Atrolnc-1 in the regulation of basal proteolysis and cytokine levels. Myosin heavy chain isoforms gene expression showed a significant decrease in the embryonic isoform and an increased tendency in type IIa isoform known as fast oxidative glycolytic fibers relatively resistant to fatigue. In animals receiving *E. coli* LPS, we observed a significant increase in the expression of pro-inflammatory cytokines and autophagy- and proteasome-related genes in limb muscles that received control AAVs. These responses were attenuated in limb muscles with Atrolnc-1 KD suggesting that this lncRNA promotes TLR4 signaling pathways possibly by modulating NFkB activity.

Conclusions:

Overall, our findings strongly support a functional role for Atrolnc-1 in regulating proteolytic pathways including the autophagy and the proteasome pathways in normal skeletal muscles. Our results also indicate that Atrolnc-1 functions as a positive modulator of TLR-4 induced inflammatory responses in skeletal muscles manifested as an increase in the production of proinflammatory cytokines and augmentation of the proteolytic pathways.

Program RESP

PI Dr. Sabah Hussain

16-51 - Factors associated with the evolution of HHV8 seropositivity in newly diagnosed people with HIV between 1997 and 2004

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The human herpesvirus 8 (HHV8), belongs to the family of DNA viruses Herpesviridae and is responsible for cancers such as Kaposi Sarcoma and B cell lymphoma as well as inflammatory Castleman's disease. The factors associated with HHV8 acquisition and immune control are poorly known in people living with HIV (PWH). Moreover, there is a raising number of cases of Kaposi Sarcoma in PWH despite antiretroviral therapy (ART). The objective of this study is to assess the influence of demographic factors and HIV clinical biomarkers on HHV8 seropositivity and specific antibody levels in newly diagnosed PWH in Montreal between 1997 and 2004.

Plasma samples were collected within 6 months of the estimated date of HIV acquisition from the primary HIV infection (PHI) cohort in Montreal. We assessed plasma levels of anti-HHV8 IgG using our in-house flow cytometry assay, which quantifies binding of IgG on phorbol-myristate-acetate (PMA) stimulated HHV8-infected BCBL1 cells. Statistical analysis was performed using non-parametric Mann-Whitney, Wilcoxon, and chi-square tests.

69 HIV-positive participants were included and the overall seropositivity was 62.3% (n=43). Seropositivity tended to be higher in men (59.0%) compared to women (33.3%) (p=0.22). Among men, those reporting sex with men (MSM) appeared to have higher seroprevalence (63.0%) compared to those with a history of intravenous drug use (IDU) (40.0%) and heterosexual men (33.3%) (p=0.4). The age of HIV acquisition had no significant effect on the seroprevalence of HHV8 (p=0.741). Although CD4 counts did not differ significantly between HHV-8 seropositive and seronegative individuals (p= 0.4769), CD8 counts were notably higher among the seropositive group (median: 878.5 cells/ μ L) compared to the seronegative group (median: 606.5 cells/ μ L) (p=0.0039), indicating that HHV8 participates in immune activation. In newly diagnosed people the rate of seropositivity slightly decreased between 1997 and 1999 (50% to 36%). Seropositivity returned back to 60% between 2001 and 2002 and a greater frequency of seropositivity was found in 2003 and 2004, with 76% and 75%, respectively. We follow people from the early stage of the infection (T1) for up to two years (T2). Out of 24 participants who remained untreated, 57.1% of individuals who were seronegative at T1 converted to seropositive status by T2. Conversely, 23.5% of those seropositive at T1 reverted to seronegative at T2. In the 19 participants who started ART, 27.2% of those seronegative at T1 became seropositive at T2 and 50% of those seropositive at T1 reverted to seronegative at T2.

The frequency of seropositivity rate tended to increase over time between 1997 and 2004. Being male and MSM was linked to higher risk of seropositivity. Early ART appeared beneficial by being linked to both a higher frequency of seroreversion to HHV8 seronegativity and a lower frequency of seroconversion to seropositivity. The influence of sex and sexual practice, early ART, and HHV8- induced immune activation on disease progression and HHV8 control should be confirmed in larger groups.

Source of funding: MCVD Summer Undergraduate Research Fellowship, McGill D2R, FRQS SIDA/MI

Program IDIGH

PI Jean-Pierre Routy

8-53 - Impact of Mineralocorticoid Receptor on the activation of TRPM7-deficient cardiac fibroblasts

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Background: Transient Receptor Potential Melastatin 7 (TRPM7) is a ubiquitously expressed ion channel bound to a kinase domain that regulates cell homeostasis by influencing intracellular Mg^{2+} levels and/or regulating signalling cascades through its kinase activity and target proteins. We previously demonstrated that TRPM7 downregulation is associated with cardiovascular inflammation and fibrosis. Here, we investigated whether activation of the mineralocorticoid receptor (MR) drives the fibrotic phenotype observed in TRPM7-deficient mice.

Methods: Hearts from wild-type (WT) and TRPM7-deficient (M7+/ Δ) mice were investigated for collagen deposition by Sirius red staining. Primary culture of cardiac fibroblasts (CF) from WT and M7+/ Δ were treated with the MR antagonist, eplerenone ($10^{-5}M$) and investigated for protein expression of fibronectin, α -SMA, TGF β , p-SMAD3, ENaC and SGK-1. Protein expression was investigated by immunoblotting.

Results: Hearts from M7+/ Δ mice exhibited collagen deposition. CF from M7+/ Δ exhibited upregulation of fibrotic markers fibronectin, which was associated with increased expression of TGF β 1 (2.14 ± 0.38 vs WT 0.25 ± 0.19), and phospho-SMAD3 (1.21 ± 0.06 vs WT 0.72 ± 0.05) and MR activation markers (ENaC and SGK1). Treatment with eplerenone indicates tendency of reducing expression of fibronectin with no changes in α -SMA.

Conclusions and perspectives. TRPM7-deficiency is associated with cardiovascular fibrosis and activation of fibroblasts. Part of these effects seem to be dependent on MR activation. Additional experiments will define the crosstalk between MR and TRPM7.

Program CHAL

PI Dr. Rhian Touyz

14-38 - Deciphering the Crosstalk between Hippo Pathway Effectors (YAP/TAZ) and E-cadherin in the Progression of Diffuse Gastric Cancer

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Background: Gastric cancer (GC) is a heterogeneous disease and ranks fifth in terms of both global cancer incidence and mortality, making it one of the leading causes of cancer-related deaths worldwide (Liu et al., 2025). According to the Lauren classification, there are two principal histological subtypes of gastric cancer: the intestinal type and the diffuse type (Ma et al., 2016). While the intestinal type is more often associated with environmental factors such as infection by *Helicobacter pylori* and displays glandular architecture, the diffuse type is characterised by poorly cohesive, de-differentiated tumour cells and is associated with a more aggressive clinical course and adverse prognosis (Zheng et al., 2006). Our research focuses on diffuse-type gastric cancer (DGC), noted for its rapid progression, metastatic potential, and resistance to standard therapies.

A hallmark of DGC is the loss of cell-cell adhesion, primarily due to methylation or mutation of the E-cadherin (CDH1) gene, which disrupts epithelial integrity and promotes tumour dissemination (Saito et al., 2017; Liu & Chu, 2014). It is hypothesised that this loss impairs activation of the Hippo pathway—a key regulator of cell proliferation and organ size—resulting in increased nuclear localisation and activity of YAP/TAZ, thereby driving tumorigenesis and resistance to cell death (Minikes et al., 2023). However, findings from our laboratory suggest that loss of YAP/TAZ itself may promote the emergence of E-cadherin-negative DGC, raising important questions about the directionality and interplay between E-cadherin loss and Hippo pathway regulation.

Aim: To address this question, we aim to investigate the correlation between E-cadherin and YAP expression in various GC cell lines and develop new DGC organoid models to further explore the roles of E-cadherin and YAP in DGC.

Methodology: The expression of E-cadherin and YAP will be studied across a panel of DGC cell lines, including MKN-1, MKN-74, AGS, OCUM-1, Kato-III, and MKN-45 by western blot, to further clarify the correlation between Hippo pathway activity and epithelial integrity, as mediated by E-cadherin. In parallel, gastric organoids derived from YAP/TAZ conditional knockout mouse models will be generated. A lentiviral approach will be employed to overexpress c-Myc, thereby transforming these organoids to model GC. To further study the role of E-cadherin, CRISPR/Cas9-mediated gene editing will be performed to knock out E-cadherin in the modified organoids. Finally, treatment with 4-hydroxytamoxifen (4-HT) will be used to induce the deletion of YAP, enabling us to study the resulting effects on organoid growth and tumorigenesis.

Conclusion: Our approach, combining genetic manipulation, organoid modelling, and protein expression analysis, provides a robust framework to elucidate the interplay between E-cadherin and Hippo pathway effectors in DGC. Whilst preliminary findings indicate a correlation between loss of YAP and reduced levels of E-cadherin in DGC, comprehensive data are forthcoming. Final results and their implications for DGC pathogenesis will be presented upon completion of ongoing studies.

Program CRP

PI Alex Gregorieff

2-11 - Effects of socioeconomic factors on the association between heat and cardiovascular hospitalizations

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Background: Climate change has become an environmental threat to human health and evidence suggests that certain subpopulations are disproportionately affected by heat-related health events. This study quantified the association between ambient temperature and cardiovascular disease (CVD) hospitalizations during summer periods in Montreal, Canada, examining the effect modification by socioeconomic factors.

Methods: We conducted a retrospective time-series analysis that utilized aggregated health, environmental and socioeconomic data for summer periods (May 1 to September 30) from 2018 to 2022, obtained from multiple regional-level data sources. Daily mean temperature-CVD hospitalization associations were assessed using quasi-Poisson regression with distributed lag non-linear model, adjusting for temporal trends, air pollution and other confounders. A multivariate meta-analysis was done to pool the effects for the 195 forward sortation areas (FSAs) within Montreal based on area-level socioeconomic variables, such as proportion of elderly (≥ 65 years old) and children (≤ 4 years old), proportion of people with no certificate, diploma or degree, and prevalence of low income. This was repeated separately for males and females to identify possible sex differences.

Results: The dataset consisted of 262,740 CVD hospitalizations; mean age 76.4 ± 14.3 years, 49.6% females and median daily temperature of 19.5°C (IQR: $15.7 - 22.7^{\circ}\text{C}$). Daily mean temperature was found to be significantly associated with CVD hospitalizations (RR = 1.15, 95% CI: 1.06 - 1.26), with a 15% increase in CVD hospitalization risk at the 99th percentile temperature (28.1°C) compared to 75th percentile reference (23°C). However, the meta-analysis revealed no significant between-area heterogeneity ($I^2 = 0\%$), indicating consistent risk patterns across Montreal's landscape. Effect modification analysis showed no significant modification by socioeconomic factors: proportion of elderly/children (RR = 1.000, 95% CI: 0.998 - 1.003), education levels (RR = 0.999, 95% CI: 0.998 - 1.001), or income levels (RR = 0.999, 95% CI: 0.998 - 1.001). These findings were similar when stratified by sex.

Conclusions: Daily mean temperature was associated with CVD hospitalizations across the FSAs, while the associations demonstrated consistent magnitude across Montreal's socioeconomic gradient. Future analyses should integrate high-resolution temperature data to capture potential finer-scale socioeconomic effect modification patterns.

Source of funding:

This study is supported by the Canadian Institutes of Health Research (CIHR), under a Catalyst Grant: Supporting research on priorities outlined in Canada's Chief Public Health Officer (CPHO) report. Additional aid is provided by Universities Canada, Community Foundations of Canada and the Rideau Hall Foundation through the Canadian Queen Elizabeth II Diamond Jubilee Scholarship.

Program CHAL

PI Dr. Louise Pilote

11-20 - Exploring Odd-skipped related 1 (Osr1) as a tumour suppressor protein in bladder cancer

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Background: The Odd-skipped related 1 (*Osr1*) gene encodes for a transcription factor essential for embryonic development. *Osr1* has been linked to the activation of p53, hinting at its role as a tumour suppressor. Additionally, downregulation of *Osr1* has been linked to various types of cancer. In bladder cancer, the uroepithelial cells undergo an epithelial-to-mesenchymal transformation (EMT) that initiates tumour progression. This process of EMT can be due to environmental exposures to cigarette smoking, workplace chemicals and arsenic in drinking water, and somatic mutations in tumour suppressor genes or oncogenes. If *Osr1* functions as a tumour suppressor gene that prevents bladder cancer, we hypothesized that overexpression of *Osr1* in bladder cancer cells would decrease cell proliferation and increase cell death. Additionally, mice heterozygous for an *Osr1* null allele would be predisposed to bladder cancer.

Methods: A human bladder transitional cell carcinoma cell line (UM-UC1), with low endogenous expression of *Osr1*, was transiently transfected with two *Osr1* constructs; one encoding *Osr1* cDNA with a Flag epitope and the other, *Osr1* cDNA with a myc epitope and an empty vector control; PCS2+ alone. Cell proliferation was assayed using antibodies directed to Ki67 in a Western Blot analysis, and cell death was evaluated using a TUNEL assay. In addition, transfected cells were also analyzed using a scratch assay: after transient transfection, a scratch was created in the monolayer, and then cells were grown over 48 hours, and migration was assessed. In parallel, mice bearing a heterozygous null mutation in *Osr1* and their wildtype counterparts were treated with 0.1% BBN for 4 months and ultrasound images were taken.

Results: Relative expression of Ki67 was found to be upregulated in the *Osr1*-myc construct but downregulated in the *Osr1*-flag construct, compared to the UM-UC1 cells transfected with the empty vector. This suggests that the *Osr1*-myc construct increases cell proliferation while the *Osr1*-flag construct decreases cell proliferation. While these results seem contrary, we speculate that this is secondary to the biological activity of the flag and myc tags. TUNEL assays show no differences in cell death between the *Osr1*-transfected cells and the control. Scratch assays are underway. Preliminary ultrasound findings from the mouse reveal that female heterozygous mice (n=4) seem to develop bladder tumours earlier than their wildtype counterparts (n=4).

Conclusions: These early results suggest that bladder cancer cells transfected with the *Osr1*-flag construct may decrease cell proliferation. Preliminary results also reveal that female mice lacking the *Osr1* allele exhibit more bladder tumours from US imaging. These results in bladder cancer cells may be limited by the low transfection efficiency observed in transient transfections; therefore, stably transfected cells are now being created.

Source of funding: CRRD Summer Scholarship, Bladder Cancer Canada

Program CHHD

PI Indra Gupta

16 - The Role of CD109 in the Etiology and Progression of Idiopathic Pulmonary Fibrosis

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Introduction: Idiopathic Pulmonary Fibrosis (IPF) is a progressive and fatal interstitial lung disease characterized by excessive scarring of the lung tissue. The etiology remains unknown, and patients face a median survival of only 3-5 years post-diagnosis. Transforming Growth Factorbeta (TGF- β) is a central mediator of fibrogenesis. It exerts its effects through both canonical (SMAD2/3) and non-canonical pathways (P38, JNK, ERK). Our team identified CD109, a GPI-anchored TGF- β co-receptor, and demonstrated its anti-fibrotic role in the skin by attenuating TGF- β signaling. However, its precise role in lung fibrosis remains unidentified. We hypothesize that CD109 plays a key role by modulating TGF- β -mediated canonical and non-canonical fibrotic pathways in IPF.

Materials and Methods: Primary human lung fibroblasts were isolated and cultured from both IPF patients and healthy donors. To investigate CD109 function, we used a lentiviral-based approach to knock down CD109 expression. Western blotting was performed to assess fibrotic responses by analyzing the expression of ECM proteins (e.g., fibronectin, collagen I) and key components of the canonical and non-canonical TGF- β signaling pathways , including phosphorylated SMAD2/3, p38, JNK, and ERK. To further delineate pathway-specific contributions, cells were treated with pharmacological inhibitors targeting SMAD signaling (SB431542) and p38 MAPK signaling (SB203580).

Results: Preliminary results indicate that CD109 knockdown leads to enhanced ECM protein expression and increased activation of both canonical (SMAD2/3) and non-canonical (p38, JNK, ERK) TGF- β signaling pathways in IPF fibroblasts.

Conclusion: Our findings suggest that CD109 is a critical negative regulator of TGF- β -mediated profibrotic signaling in IPF lung fibroblasts.

[Link to PDF](#)

Program SIS

PI Dr.Anie Philip

16-52 - Assessing Varicella Zoster Virus Immunity in Immunocompromised Adults on Biologic Therapies

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Varicella zoster virus (VZV) is a highly contagious virus responsible for two clinical manifestations; primary varicella (chickenpox) and reactivated herpes zoster (shingles). VZV is most prevalent in children but poses a significantly greater risk such as life-threatening complications to older age groups and immunocompromised patients. Previous studies, including studies from our laboratory, have demonstrated that some pediatric patients undergoing biologic treatment remain susceptible to VZV. However, whether this is applicable to an adult population remains unanswered. This raises concerns about the potential impact of biologic therapies on VZV immunity.

Although self-reported VZV infection history has been generally correlated with seropositivity in adults, there is no guarantee whether this is still the case for those undergoing immunosuppressive biologic therapy. This project aims to study the effects of biologic treatments on the immunity status of VZV in adult immunocompromised patients.

The patient cohort that will be studied is part of Centre Transdisciplinaire de Thérapies Biologiques (CTTB) biobank and registry, specifically, a group of patients with Inflammatory Bowel Disease (IBD) on biological therapies (n=65). In addition, a control group without immune conditions or immunosuppressive treatment (n=35) will be used as control to assess the immunity status to VZV. An enzyme-linked immunosorbent assay (ELISA) will be performed using serum samples for anti-VZV antibody quantification with envelope glycoprotein E (gE) antigens. The VZV strains used will be OKA (vaccine) and Wild type (recombinant).

Given the known immunomodulatory effects of biologic therapies, we anticipate that some adult patients in the IBD cohort on biologic treatments will exhibit reduced immunity to VZV infection than the controls. This would emphasize the importance of monitoring serology status before, during, and after biologic treatment and support the importance of the booster VZV vaccine in adult compromised patients.

Funding is provided by the Montreal Children's Hospital Foundation and the Canada Summer Jobs wage subsidy program.

Program RESP

PI Christine McCusker

16-50 - Clinical Impact of Human Papillomavirus, p53, and p16 Status in Vulvar Cancer: Insights from a Retrospective Single Site Study

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Background:

Vulvar squamous cell carcinoma (VSCC) is a rare malignancy, accounting for approximately 5-6% of all gynecologic cancers. While the median age at diagnosis is 70 years, recent trends show a rising incidence among younger women. Historically classified by the presence or absence of human papillomavirus (HPV) infection, VSCC is now increasingly recognized as a heterogeneous disease with distinct molecular subtypes. A newer classification framework includes three subtypes: HPV-associated, HPV-independent p53 wild-type (p53wt), and HPV-independent p53 abnormal (p53abn), each with potentially different clinical behaviors and prognoses. Early studies suggest that HPV-associated tumors are linked to more favorable outcomes, whereas p53abn tumors may exhibit more aggressive features and poorer survival. Additionally, p16 is an excellent immunohistochemical surrogate to detect the HPV integration within tumor tissue. Despite these insights, molecular subtyping is not yet routinely integrated into clinical management, and its prognostic utility remains underexplored in Canadian cohorts. This study aims to evaluate the clinical and pathological impact of HPV and p53 status in patients with VSCC, with the goal of informing more personalized, risk-adapted treatment strategies.

Methods:

We are completing a retrospective cohort study including all women with histologically confirmed VSCC treated between 2003 and 2024 at the Royal Victoria Hospital. Patients with vulvar cancer of other histology subtypes, or with less than 6 months of follow-up data, were excluded. 111 eligible patients were identified through hospital records, and relevant clinical, histopathological, treatment, and outcome data are extracted from electronic medical records. Outcomes of interest include demographics, tumor characteristics, HPV/p53/p16 status, treatment details, and outcomes (recurrence, survival). Data will be analyzed using quantitative data analysis, including statistics, chi-square and t-tests, Kaplan-Meier survival curves, log-rank tests, and Cox proportional hazards models to evaluate associations between molecular subtype and clinical/pathological outcomes.

Anticipated Results:

Data collection and analysis are currently in progress. We anticipate that HPV-associated VSCC will demonstrate distinct clinicopathological features such as smaller tumor size, lower grade, fewer nodal metastases, and association with intraepithelial precursors compared to HPV-independent subtypes. Within the HPV-independent group, we expect p53 abnormal tumors to exhibit more aggressive characteristics, including increased depth of invasion, higher tumor grade, and worse recurrence-free survival, disease-specific survival and overall survival, when compared to p53 wild-type cases. We also anticipate that immunohistochemical p16 and p53 status will correlate strongly with HPV genotyping results and serve as reliable surrogate markers in routine diagnostic practice.

Conclusion:

Integrating HPV and p53 status into the evaluation of vulvar squamous cell carcinoma (VSCC) holds promise for refining prognostic assessment beyond traditional clinical and pathological parameters. Anticipated findings may support the incorporation of a biomarker-based classification system into Canadian treatment guidelines, enhancing risk stratification and informing both in treatment intensity and follow-up strategies. Given the risk of morbidity and significant impact on quality of life of current treatments, this molecular approach may help personalize care, reduce adverse effects, and improve long-term outcomes.

Program CRP

PI Annie Leung

1 - Comparing Motor and Visual Cortex Layer-6 Microcircuits with 2-Photon Optomapping

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Introduction: The structure of neocortical microcircuits determines its function. Therefore, the structure of a sensory input area such as primary visual cortex (V1) is expected to differ from that of an output area such as primary motor cortex (M1). However, mapping circuits with synaptic resolution is prohibitively slow with state-of-the-art electrophysiology such as multiple patch. We therefore implemented optomapping—a 100x faster technique—to investigate connectivity and synaptic dynamics. Here, we focused on layer (L) 6 of M1 and compared its organization to L6 of V1. Specifically, we explored excitatory inputs onto pyramidal cells (PCs) as well as onto basket cells (BCs) and Martinotti cells (MCs), two major inhibitory cell classes that mediate late and early onset inhibition, respectively.

Methods: To express the ChRME opsin in PCs, we injected a Cre-dependent virus into the cortex of neonatal Emx1-Cre mice. At postnatal day (P)18-26, we made acute sagittal brain slices containing either M1 or V1. We performed whole-cell patch-clamp recordings of L6 PCs, MCs, and BCs, while stimulating opsin-expressing candidate presynaptic PCs. We used femtosecond laser spiral scans at 1040nm to drive candidate presynaptic PCs in a cortical column and across L6, allowing for efficient connectivity mapping with single-cell precision. Stimulus-locked EPSPs in the patched cell were used to determine connectivity, synaptic strength and dynamics. We classified recorded cells as a PC, BC, or MC based on morphology and electrophysiology.

Results: Preliminary results from L6 PCs revealed that connectivity rates depended on presynaptic layer (generalized linear mixed model - GLMM: $p < .001$), but not on neocortical area ($p = 0.25$). In V1 and M1, L6 PCs received more PC input from within L6 compared to L2/3 ($p < .001$), L4 ($p < .001$), and L5 ($p < .01$). Synaptic strength depended on both layer and neocortical region (LMM: $p < 0.05$). Specifically, M1 L6 PCs received stronger connections from L5 PCs than from L4 PCs ($p < .05$). Lateral connectivity rates between V1 and M1 L6 PCs were indistinguishable (GLMM: $p = .17$).

Conclusions: Despite gross structural similarities between V1 and M1, we found microcircuit-level differences across layers, which may reflect distinct functionalities. Our findings support the idea that common organizing principles—such as target-cell-dependent short-term plasticity and modular microcircuit motifs—are preserved across cortical regions.

Program BRAIN

PI Per Jesper Sjöström

6-38 - Low-penetrance dominant diabetes due to *ABCC8* variants in antibody-negative patients diagnosed with type 1 diabetes (T1D)

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Background and Hypothesis: Maturity-Onset Diabetes of the Young (MODY) is a rare, autosomal dominant, non-autoimmune form of diabetes caused by single-gene mutations, including in *ABCC8*, a key regulator of insulin secretion. Exome sequencing of 350 antibody-negative type 1 diabetes (T1D) patients by the ADDAM project (Accurate Diagnosis in Diabetes for Appropriate Management) revealed 15 carriers of rare *ABCC8* variants. This is substantially more than expected considering the known prevalence of *ABCC8*-MODY, believed to be extremely low. Moreover, these patients lack a family history characteristic of dominant monogenic disease. We hypothesize that these *ABCC8* variants cause low-penetrance monogenic diabetes only in individuals with genetically determined fragile or malfunctioning pancreatic beta cells. We further hypothesize that much of this vulnerability is due to an elevated burden of type 2 diabetes genes.

Methods: We began by statistically confirming that our observed excess of *ABCC8* variants is not the result of chance by performing a mutation-burden analysis. Ethnicity-specific variant frequencies in the general population were extracted from the GnomAD v4 database. A Monte Carlo Variant Burden Test was then performed by simulating one billion random cohorts of 350 individuals, with expected variant counts sampled according to population allele frequencies. An empirical p-value was calculated as the proportion of iterations in which the simulated number of variant alleles equalled or exceeded that observed in our cohort. For variants absent from GnomAD, we conservatively estimated population frequencies by approximating their upper 95% confidence bound. Based on array genotyping and TOPMed imputation, we also calculated the T2D polygenic risk score (PRS), which will be compared with that of antibody-confirmed T1D controls.

Results: Simulations based on GnomAD frequencies consistently produced far fewer *ABCC8* variant alleles than observed in the ADDAM cohort. The mean simulated allele count was 2.7 (95% CI: 0-6), and only 28 of one billion simulations produced ≥ 16 variant alleles ($p = 2.8 \times 10^{-8}$), indicating a significant enrichment. This satisfies the statistical significance threshold of 2.5×10^{-6} , correcting for the number of known human genes (0.05/20,000). The mean T2D PRS was 1.3, higher than the theoretical general population mean of 1.0. Statistical comparison with antibody-positive T1D controls is underway.

Conclusion: Our results provide strong statistical evidence that rare *ABCC8* variants are significantly enriched in antibody-negative patients diagnosed with T1D, relative to the general population. This supports the hypothesis that such variants cause low-penetrance diabetes that require additional genetic risk factors. We are now poised to test the hypothesis that such background genetic risk factors largely overlap with polygenic T2D variants through comparison to antibody-positive T1D controls.

Source of Funding: The ADDAM project is funded through CIHR grants. The presenting author received funding through the Dr. Harry I. Cramer Research Scholarship, as part of McGill's Summer 2025 Research Bursary Program.

Program CHHD

PI Constantin Polychronakos

2-12 - Investigating the Extent of Surround Suppression

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Background: Amblyopia is a neurodevelopmental binocular vision disorder characterized by abnormal interocular suppression of the weaker amblyopic eye by the stronger fellow eye. Conventional treatments have shown some promise, but do not address the associated challenges with binocular vision. This study aims to investigate the extent of interocular suppression mechanisms in amblyopes using a center-surround masking paradigm. Furthermore, the extent of intraocular suppression will be tested and compared to the interocular data. As a first step, only control individuals were tested to establish a baseline with the hopes of developing novel, more effective amblyopia treatments. It is hypothesized that the strength of suppression will decrease with increasing eccentricity of a surround mask.

Methods: A standard psychophysical contrast detection task (2IFC) was administered to control individuals. Stimuli consisted of a central grating (target) and a surrounding ring (mask). Both the target and ring were vertically oriented sinusoidal gratings. We tested both low (0.25 cycles/degree) and medium (1 cycles/degree) spatial frequencies. In each trial, participants were shown two stimuli in randomized order: the target and ring together or the ring alone. Their task was to identify which stimulus contained the target. Contrast detection thresholds were measured at three different surround eccentricities: near, intermediate and far. Furthermore, for each eccentricity, two target configurations were tested: monocular (target and ring were presented to the same eye) and dichoptic (target and ring were simultaneously presented to separate eyes).

Results: Preliminary results show that the detection thresholds decrease with increasing surround eccentricity. This was particularly evident in the dichoptic viewing conditions, which served as a direct measure of interocular suppression. This trend indicates a potential inverse relationship between suppression strength and surround mask eccentricity for both stimulus configurations.

Conclusions: Based on the preliminary findings, standard threshold levels at various mask eccentricities have been established for control individuals. Literature in this field has demonstrated that at various eccentricities, different cerebral structures are responsible for inducing the suppression. Thus, in comparing amblyopic to the obtained control results, it could allow for better isolation of the impaired brain region thus creating new targets for novel therapies.

Source of Funding: This research project was made possible thanks to the generous support of the Sir Edward W. Beatty Memorial scholarship and the Visual Sciences Research Network.

Program BRaIN

PI Alexandre Reynaud

7-45 - Tripod: Trimodal Methylation Detection from Nanopore Data using Deep Learning

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Background: DNA methylation is an epigenetic modification that plays a critical role in genomic imprinting, transposon suppression, and gene regulation. Accurate detection of methylation is therefore essential in many areas of biomedical research. Nanopore sequencing, a third-generation technology, enables real-time, long-read sequencing of native DNA and is increasingly adopted in epigenetic studies. The changes in ionic current produced as single-stranded DNA passes through a protein nanopore are used to infer bases and modifications. All existing Nanopore methylation detection tools rely solely on the nucleotide sequence and/or raw signal data. Here, we present Tripod, a deep learning model that utilizes one additional modality, frequency-domain features derived from continuous wavelet transformation of the raw signal, and integrates the three modalities using contrastive learning for improved methylation detection from Nanopore sequencing data.

Methods: Tripod takes three input features: (1) a 61bp sequence centered on the candidate base, (2) the corresponding raw signal, and (3) the matching scaleogram segment from wavelet transformation. The architecture consists of three modality-specific encoders and a classification module. The sequence encoder is DNABERT2, the signal encoder is a vanilla Transformer, and the scalogram is encoded by a convolutional neural network (CNN). The outputs from each encoder (CLS token from signal and sequence encoders and globally averaged output from the final CNN layer) are concatenated and fed into the classification module, which outputs a modification probability for the target base. Model training is performed in two phases. In Phase 1, the signal and sequence encoders are pretrained using masked token prediction. Phase 2 involves both contrastive learning and supervised learning, using a composite loss function that combines contrastive loss and cross-entropy loss.

Results: We first evaluated single-modality results for 5mCpG per-read detection. The raw signal modality alone achieved an F1 score of ~90%, while the sequence modality produced an F1 score of ~78%. When using the frequency-domain features alone, the model achieved an F1 score of ~82%. Integrating all three modalities improved per-read 5mCpG detection performance to an F1 score of ~92%, outperforming DeepMod2, a state-of-the-art methylation detection tool, trained on the same dataset.

Conclusions: Our results underscore the value of incorporating frequency-domain features for methylation detection from Nanopore data, as they contain informative patterns relevant to DNA methylation. We show that contrastive learning effectively integrates modalities and facilitates representation learning. Our framework is also adaptable and can be extended to other types of DNA modifications where reliable detection tools are currently limited.

Source of Funding: This work is supported by the Canadian Institutes of Health Research (CIHR) (PJT-180505 to J.D.) and the Fonds de recherche du Québec - Santé (FRQS) (295298 to J.D. and 295299 to J.D.). The presenter was awarded the NSERC Undergraduate Student Research Award (USRA) for summer 2025.

Program RESP

PI Jun Ding

12-25 - Characterization of Prolactin Induced Phenotypic Changes in Triple-Negative Breast Cancer Patient-Derived Xenografts

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Introduction: Triple-negative breast cancer is an aggressive subtype of breast cancer with limited targeted treatment options and poor prognosis. Our lab's findings suggest that prolactin, known for its role in normal mammary gland development, suppress tumorigenicity in TNBC by promoting tumor cell differentiation and reducing stemness. Our goal is to look at how PRL treatment influences the expression of differentiation, proliferation, and stemness markers in TNBC patient-derived xenograft (PDX) tumors and complementary in-vitro assays in TNBC cell lines.

Methods: Immunodeficient NSG mice were transplanted with TNBC PDX tumors and treated with recombinant human PRL or vehicle control. After treatment, tumor tissues were collected and processed for immunohistochemistry. IHC staining is being performed for markers: Vimentin (mesenchymal marker), CK18 (luminal marker), Ki67 (proliferation marker), CD44 (stemness marker), Estrogen Receptor (ER), CK14, and CK5/6. Stained sections will be imaged and quantified using QuPath to assess differences in marker expression between PRL-treated and control groups. TNBC cell lines (MDA468) will also be treated with PRL in vitro and analyzed for the same markers by Western blotting to validate IHC results.

Results: To examine PRL effects in TNBC tumor growth, we used 2 PDX models of TNBC (obtained from The Jackson Laboratory): TM00999 (Grade 3) and TM00096 (Grade 3). Following transplantation and upon tumor size reaching palpable, mice were separated into 2 groups of equal tumor size at the outset of treatment, establishing a reliable baseline for evaluating therapeutic effects. Remarkably, PRL treatment (intraperitoneal (IP) injections efficiently reduced tumor volume/growth across all individual mice over time in the 2 TNBC PDX models. At experimental endpoint, tumor weight also showed significant decrease in the PRL treated group. Furthermore, none of these animals exhibited any apparent adverse effects (reduced weight, hair loss, health issues), suggesting little or no toxicity of PRL *in vivo*. Interestingly, we also found that PRL treated endpoint tumors were enriched with differentiated EpCAM⁺ cells compared to untreated tumor samples emphasizing the differentiation effects of PRL in TNBC. We are currently staining and analyzing the samples. We anticipate that PRL-treated tumors will show reduced expression of mesenchymal (Vimentin), stemness (CD44) and basal markers (CK5/6, CK14), decreased proliferation (Ki67), and increased luminal differentiation markers (CK18, ER).

Conclusions: These results support the hypothesis that PRL promotes differentiation and shifts tumor cell population toward a less aggressive, more differentiated phenotype in TNBC associated with tumor downstage. Moreover, understanding these tissue level changes highlight PRL's potential as a differentiation-based therapy.

Program CRP

PI Suhad Ali

14-39 - Senotherapeutics Prevent Disc Degeneration and Back Pain

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Introduction: Low back pain is experienced by ~ 80% of individuals at some time in their lives and is globally the number one cause of years lived with disability. This age-related health problem is often associated with intervertebral disc (IVD) degeneration. Despite the prevalence, little is known about the molecular mechanisms leading to IVD degeneration and its associated pain. There is growing recognition that senescent cells accumulate with ageing and during tissue degeneration, where they contribute directly to disorders including heart disease, cancer, and osteoarthritis. The goal of this study is to evaluate the potential of senolytic components as a preventive approach for IVD-related low back pain.

Methods: Treatment of *sparc*^{-/-} mice began at 3-4 months of age right when the animals start to show signs of intervertebral disc (IVD) degeneration and low back pain. All experiments were approved by the Animal Care Committee of McGill University and followed the guidelines of the Canadian Council on Animal Care. The animals received weekly oral gavage treatments for five months with RG-7112 and O-vanillin, or a combination of both, to evaluate if treatment prevented the progression of painful IVD degeneration. High-resolution micro-CT scans of the spine were conducted to evaluate IVD volume, vertebral bone, and endplate health.

Results: Micro-CT analysis showed lower bone quality and disc volume in *sparc*^{-/-} compared with wild-type mice. Single-drug treatment increased bone volume, bone/tissue volume (BV/TV), trabecular thickness, and trabecular number. The combination of both drugs showed a greater improvement in these parameters. Furthermore, senolytic treatment reduced the BV/TV percentage in the endplate, with the combination treatment providing an additive effect. Our findings also revealed that single-drug treatment resulted in a trend towards improved disc volume compared to vehicle-treated mice, while the combination treatment resulted in a significantly higher disc volume.

Discussion and significance: Recent reports on senolytics therapies suggest that combining O-vanillin and RG-7112 to target different pathways can improve treatment outcomes. Our findings suggest that senolytics can enhance disc volume, and improve bone, disc, and endplate health in *sparc*^{-/-} mice, which are known to have osteopenia. Relatedly, systemic oral treatment of O-vanillin and RG-7112 alleviates degenerative changes in tissues across the spine and spinal cord indicating that they can provide novel therapies for LBP and related painful disorders.

Source of funding: This project is supported by CIHR, Arthritis Society, AOSpine Research Network, Shriners Hospital and RSBO.

Program SIS

PI Lisbet Haglund

13-32 - Improving Pre-operative Emotional Distress Shortens Hospitalization for Esophagectomy

Nisha Suarez¹

¹McGill

Background

Pre-operative emotional distress - characterized by anxiety, depression, and/or psychological stress - is commonly experienced by patients diagnosed with esophageal cancer. Previous studies have observed that emotional distress is associated with longer hospital length of stays (LOS) in various cancer populations, including esophageal cancer. However, the impact of changes in emotional distress during the pre-operative period on post-operative LOS remain unclear. This exploratory study aims to test whether improvements in pre-operative emotional distress influence post-esophagectomy LOS.

Methods

We conducted a retrospective analysis using data collected from a high volume North American tertiary care referral centre. Eligible participants completed the Functional Assessment of Cancer Therapy-Esophageal (FACT-E) at (1) diagnosis and (2) prior to esophagectomy. Emotional distress was measured using the FACT-E Emotional Well-Being (EWB) subscale. Changes in EWB scores between the two time points were categorized as “improved” or “unimproved” (i.e., stable or decreased). The Mann-Whitney U test was used to test the associations between LOS and the “improved” / “unimproved” EWB category.

Results

Of the 106 participants that completed the FACT-E at both time points and had an LOS related to esophagectomy, 67 (63%) were categorized as “improved”. Those in the “improved” category experienced an average increase of 5.1 points in the EWB subscale score. The “improved” group had an average LOS of 9.2 days compared to 10.4 days for the “unimproved” group ($p < 0.05$).

Conclusion

Improvements in EWB score - used as a proxy for emotional distress - during the pre-operative period was associated with shorter postoperative LOS for esophageal cancer patients. The average difference was more than a full day. This suggests that emotional distress, if improved, can directly influence early outcomes and post-esophagectomy recovery. Future research should investigate the impact of pre-operative psychological assessments and interventions to better understand emotional distress as a modifiable risk factor for esophagectomy outcomes.

Program SIS

PI Trafford Crump

13-28 - Validity and Acceptability of the Shoebox Tablet-Based Audiometer in School-Aged Children

Ninell Sygal¹

¹RI-MUHC

Background

Around 7.7% of Canadian youth aged three to nineteen are estimated to have hearing loss, most of which is mild and unilateral. Etiologies in children include infections, congenital malformations, exposure to high-intensity sounds, and most predominantly genetic factors.

Currently, no universal newborn hearing screening is implemented in Quebec. Consequently, hearing loss is often diagnosed only once children reach the age of two, and non-severe cases frequently go undetected until school age. Unaddressed hearing loss can therefore lead to significant learning and literacy delays, as well as communication difficulties. Shoebox is a tablet-based audiometer that allows patients to perform a hearing test in the form of an interactive iPad game. Because it is quick, portable and child-friendly, we believe this device can help reduce undetected hearing loss in children. Although its reliability and efficacy have been explored in the literature, the feasibility of deploying this tool on a wider scale is less well characterized.

Objective

The objectives of this study are to 1) determine parental and patient acceptability of the Shoebox audiometer as a hearing screening tool and to 2) compare it to the standard hearing test performed at the Audiology Clinic of the Montreal Children's Hospital. The long term goal is to evaluate the potential of tablet-based play audiometry tests and to determine if the Shoebox tablet-based audiometry could potentially serve as a reliable screening tool for hearing loss in children.

Methods

We will analyze the data collected between 2017 and 2019 of approximately 300 children between the ages of 4 to 12 years old who randomly agreed to participate and undergo Shoebox audiometry during school visit. Children with suspected hearing loss, or abnormalities, were referred to undergo formal testing at the MCH Audiology Clinic. We will also analyze the demographic information of participants to determine if there is variability in test compliance, abnormal test results, or other variables across different subgroups.

Results

We anticipate that children who screen positive for hearing loss using the Shoebox audiometer will also demonstrate abnormal results on formal audiology testing. Additionally, we expect the Shoebox screening to be well-accepted across various demographic groups, with older children showing higher compliance and completion rates compared to younger children.

Program CHHD

PI John J. Manoukian

6-39 - Maintaining The Phenotype of Primary Human Ligament Cells Using Physiological Oxygen Tensions for Tissue Engineering Applications

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INTRODUCTION: Anterior cruciate ligament injuries are amongst the most common musculoskeletal injuries. However, the current standard of care, ligament reconstruction surgery, suffers high failure and revision rates. Thus, there is a significant need for an alternative solution. Tissue engineering presents a compelling alternative by aiming to create functional bioengineered ligament grafts, yet it faces challenges such as poor graft integration, optimal culture conditions, and securing viable cell sources. Cell-seeded bioengineered constructs are superior to cell-free ones. The use of primary human ligament cells for ligament regeneration presents two limitations: the limited number of cells upon isolation and their dedifferentiation during *in vitro* expansion. By overcoming these limitations, we would be able to bioengineer ligament implants to be used in ACL-R, which would enhance surgical outcomes. In addition, ligament tissues receive lower oxygen tensions compared to other tissues, which is optimal for tissue physiology and the integration of bioengineered grafts. If developed in non-physiological culture conditions, these grafts will face “adverse conditions” and poor tissue integration. Our hypothesis states that in optimized near physiological oxygen tensions, the culturing of primary human anterior spinal ligament cells would prevent unwanted dedifferentiation and maintain their primary ligamentogenic phenotype for tissue engineering and regenerative medicine applications.

METHODS: Human anterior spinal ligament tissues were obtained from deceased donors per the institutional ethics board-approved protocols. Primary ligament cells were isolated from resected samples by enzymatic digestion. Primary human spinal ligament cells were expanded for 10 days at 37°C under three different oxygen tensions: standard cell culture oxygen tension (20% O₂), intravenous (5% O₂), and intraarticular (2% O₂). Cell-seeded culture plates were placed in a standard incubator with 5% CO₂ at 37°C for 20% O₂. For 5% and 2% O₂, hypoxia incubator chambers (StemCell Technologies) were sealed and flushed with gas premixes, respectively, and placed inside an incubator at 37°C for the duration of the experiment. The media was changed every 3 days, and the hypoxia chambers were resealed and reflushed. At the end of the incubation period of 10 days, the relative gene expression of ligament markers, cell viability, growth rate, and metabolic activity were assessed.

RESULTS: Our data show that 5% oxygen tension does not affect the viability of primary ligament cells. Growth rate analyses show that near physiological oxygen tensions promote cell growth and population doubling. Moreover, qPCR results indicate higher levels of collagen type-1 and type-3, tenascin C, and scleraxis expression in primary human ligament cells cultured under 5% and 2% O₂.

CONCLUSION: Our results suggest that near-physiological culture conditions maintain the ligamentogenic phenotype of primary human spinal ligament cells. Therefore, we propose culturing our bioengineered, cell-seeded ligament grafts under these conditions to promote robust tissue development and better prepare the grafts for integration into the intraarticular environment upon implantation.

Program SIS

PI Rahul Gawri

3 - Regulation of Iron Metabolism and Mitochondrial Health in Diabetic Cardiomyopathy: Therapeutic Potential of Chinese Herbal Medicine

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Running title: Iron metabolism and mitochondrial quality control in diabetic cardiomyopathy

Background: Diabetic cardiomyopathy (DCM) is a common diabetes-related complication that can progress to heart failure. Early-stage DCM is asymptomatic, requiring advanced imaging for diagnosis, and currently lacks approved targeted therapies, highlighting the urgent need for DCM-specific drugs. Emerging evidence suggests that iron homeostasis imbalance and mitochondrial dysfunction are closely interconnected and synergistically drive DCM onset and progression.

Methods: This review systematically explores the molecular interplay between ferroptosis and mitochondrial damage in DCM and assesses the therapeutic potential of three intervention categories: 1. Standard glucose-lowering agents, 2. Novel mechanism-targeted therapies (iron chelators, mitochondrial protectants), 3. Multi-targeting Chinese herbal medicines and their bioactive constituents

Results: While SGLT-2 inhibitors and other antidiabetic drugs provide modest protection against DCM progression, they fail to fully restore mitochondrial function. Emerging targeted therapies such as iron chelators and mitochondrial protectants face safety concerns and lack extensive clinical validation, with their potential drug-drug interactions remaining uncertain. In contrast, resveratrol (a herbal monomer) and Qishen Yiqi Dripping Pills (a Chinese patent medicine) regulate multiple ferroptosis and mitochondrial pathways, helping mitigate diabetic myocardial injury. Resveratrol has established glycemic benefits and safety in numerous clinical trials, while Qishen Yiqi is currently under clinical evaluation. Additional herbal agents with demonstrated efficacy in ferroptosis and mitochondrial function are also reviewed.

Conclusions: Given the multifactorial nature of DCM, combination therapies targeting ferroptosis and mitochondrial dysfunction may offer superior outcomes. Future drug development should prioritize agents—whether synthetic or natural—that precisely regulate these interrelated pathways, enabling personalized treatment strategies for DCM.

Funding

This work was supported by the National Administration of Traditional Chinese Medicine Young Qi Huang Scholars Support Project [National Traditional Chinese Medicine Human Education Development (2020) No. 7]; the High Level Chinese Medical Hospital Promotion Project [No. HLCMHPP2023084]; the Beijing University of Chinese Medicine Leading Talent Training Program; and the National Key R&D Program of China [2024ZD0523503].

Program MeDiC

PI Jun-Li, Liu

7-46 - Characterizing clinically relevant Cancer-Associated Fibroblast (CAF) subtypes in Gastroesophageal Adenocarcinoma

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Introduction: Gastroesophageal adenocarcinoma (GEA), the most common esophageal malignancy in North America, ranks among the most aggressive cancers globally; 5-year survival is <20% due to late diagnosis, genomic heterogeneity, and widespread resistance to the only systemic standard of care available, docetaxel-based triplet chemotherapy. Emerging evidence implicates the tumor microenvironment (TME), particularly cancer-associated fibroblasts (CAFs), in progression and treatment failure. Here, we investigate the heterogeneity and functional roles of CAF subtypes in GEA, aiming to identify populations that evade chemotherapy-induced cell death, exhibit phenotypic plasticity, contribute to chemoresistance, and represent potential targets for stroma-directed therapies.

Material and Methods: GEA patients who provided informed consent and were scheduled to receive four cycles of neoadjuvant chemotherapy (FLOT regimen; 5-FU, Leucovorin, Oxaliplatin, Docetaxel) were selected for the study. Primary fibroblasts were isolated from tumor and adjacent normal tissue specimens collected before, on- (after two cycles) and post-chemotherapy (after four cycles), then expanded in culture. Portions of these same tissue samples were also subjected to single-cell RNA sequencing (scRNA-seq). Following cell type deconvolution, predominant CAF subtypes were identified. Two specific CAF subtypes were further characterized and validated *in vitro* using immunofluorescence (IF) staining. Briefly, fibroblasts were fixed, permeabilized, and stained with primary antibodies: PDGFR- α (Cell Signaling Technology #3164), α -SMA (Abcam, ab124964), and Vimentin (Sigma-Aldrich V6630); followed by secondary antibodies: donkey anti-Rabbit Alexa Fluor 555 (ThermoFisher A-31572) and donkey anti-Mouse Alexa Fluor 488 (ThermoFisher A-21202). Imaging was performed using EVOSTM M7000 and Zeiss LSM780 confocal microscopy. CAF subtype ratios were quantified using ImageJ analysis software. In a secondary arm of the study, both treatment-naïve and on-treatment fibroblasts (including CAFs and normal-associated fibroblasts/NAFs) were assessed for intrinsic cell death *via* senescence.

Results: Single-cell RNA sequencing analysis identified two clinically relevant and predominant CAF subtypes in GEA: inflammatory CAFs (iCAFs) and myfibroblastic CAFs (myCAFs). Preliminary analysis suggests that the iCAF-to-myCAF ratio changes throughout the treatment trajectory (potential plasticity) and may correlate with treatment outcomes. ***PDGFR α ⁺ α -SMA⁻*** iCAFs and ***PDGFR α ⁻ α -SMA⁺*** myCAFs exhibit distinct cell fates and transcriptional profiles across the treatment timeline. Initial IF staining, assessed by phase-contrast and fluorescence imaging, confirmed the presence of these two morphologically distinct fibroblast subpopulations *in vitro* in both treatment-naïve and on-treatment (post-cycle 2) cultures. These findings support the co-existence of iCAF and myCAF populations in tumor-derived fibroblast cultures. Ongoing quantitative analysis and senescence based-cell death assays are expected to further delineate the functional differences between these CAF subtypes.

Conclusions: This study demonstrates the utility of scRNAseq- and immunofluorescence-based approaches to characterize and quantify CAF heterogeneity *in vitro* using patient-derived fibroblasts from GEA. The data reveal inter- and intra-patient-specific diversity and dynamic plasticity of fibroblast subtypes during chemotherapy in GEA. Understanding CAF composition and behavior may inform future strategies to therapeutically modulate the tumor stroma. Additionally, this project establishes a scalable platform for training and collaboration within the Cancer Research Program and supports broader precision oncology initiatives.

Program CRP

PI Lorenzo Ferri

13-33 - Developing a Framework to Evaluate the Impact of Patient Engagement in Esophageal Cancer Research

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Background:

Involving patients in developing clinical research studies has demonstrated to improve its relevance, feasibility, and accessibility. As a result, a number of research networks have been established to engage patients in various stages of the research process. While these have been supported through conceptual frameworks, they lack clear evaluation parameters against which their effectiveness can be judged. This study is aimed at addressing this knowledge gap. The purpose of this study is to create the first known patient research network dedicated to esophageal cancer and to develop an evaluation framework with which this network's activities can be assessed.

Methods:

The methods undertaken in this paper can be divided into three steps. First, the high-level goals of the patient engagement network were established based on our own interests in this project. Next, a comprehensive search of the literature for existing patient engagement models was performed using Google Scholar and PubMed using the MeSh terms "Esophageal Neoplasms", "Patient Participation", and "Research". We also met with existing esophageal cancer advocacy organizations to receive constructive feedback on our goals and engagement model. Finally, we established operational definitions of core components of our framework that will be used to measure the effectiveness of this network's activities.

Results:

We established the Esophageal Cancer Patient Network (ECPN). Goals and scope of the ECPN were established through a Terms of References, which included its purpose, member roles and responsibilities, meeting schedule and structure, confidentiality, and ethical considerations. These are made publicly available on the ECPN website. The literature search yielded 10 results. These were reviewed and adapted to meet our specific needs, as laid out in the ToR. Constructive feedback was given by two advocacy networks. Finally, we set three measures of effectiveness: 1) member engagement, as measured through meeting attendance and views of our outreach channels; 2) output from our study development and study interpretation sub-committees; and 3) member satisfaction, as measured through a bi-annual survey.

Conclusions:

Engaging patients in clinical research is an important component to ensuring that this research is patient centered. While there are plenty of conceptual frameworks to help establish this kind of engagement, none of them have been defined operationally to provide objective measures of their implementation. We have done that with the ECPN; not only establishing the first patient engagement network in esophageal cancer but also setting new standards for measuring how effective we are at including them in the research and dissemination process.

Program SIS

PI Trafford Crump

12-26 - Characterization of *ekl-7* as a potential Enhancer of RNAi

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Abstract:

Introduction: *Caenorhabditis elegans* is a powerful model for studying conserved genetic pathways due to its unique combination of cellular complexity and genetic simplicity. One of the most informative tools in *C. elegans* research is RNA interference (RNAi), which enables systemic gene knockdown. Exogenously introduced double-stranded RNA (dsRNA) is diced into short interfering RNAs (siRNAs) that mediate effective post-transcriptional and transcriptional gene regulation. The efficiency of RNAi is regulated by *eri* (Enhanced RNAi) genes, which normally regulate endogenous small RNA pathways to balance gene expression. Mutations in these *eri* genes increase *C. elegans*' sensitivity to exogenous dsRNA, enhancing RNAi effectiveness. Our lab discovered that endogenous small RNA pathway components promote Ras/MAPK signaling during specification of the excretory duct cell (EDC) fate. One such component, the *Kinase Suppressor of Ras-1* (*ksr-1*) and *ksr-2* genes, which encodes functionally redundant protein scaffolds. Mutations in *ksr-1* are 99% wild type, but animals that fail to specify the EDC have defects in osmoregulation and die with a distinct larval "rod-like" lethal phenotype. A genome-wide RNAi screen identified 18 genes that enhanced the *ksr-1*-mediated rod-like lethality phenotype. These enhancer of *ksr-1* lethality (*ekl*) genes encode proteins involved in gene expression including regulators of endogenous small RNA pathways. However, the specific functions of the *ekl-7* gene remain largely uncharacterized.

Materials and Methods: In this study, we tested whether *ekl-7* functions as an *eri* gene. To test this, we used RNAi-based gene knockdown via dsRNA feeding and assessed RNAi sensitivity. Mutations in *hmr-1* (E-cadherin) cause 100% embryonic lethality, however *hmr-1* RNAi is inefficient. We performed *GFP* RNAi (negative control) and *hmr-1* RNAi in wild-type, *rrf-3* (an *eri* mutant, positive control) and *ekl-7* mutant strains: *ekl-7(vh48)* (null mutation) and *ekl-7(vh20)* (missense mutation, E422K). We then quantified knockdown efficacy by measuring the percentage of unhatched eggs relative to the total number of eggs laid.

Results: Our preliminary results suggest that the two *ekl-7* alleles differentially modulate sensitivity to *hmr-1* RNAi. Specifically, the *ekl-7(vh20)* mutant that demonstrated increased sensitivity to RNAi, as evidenced by a higher percentage of unhatched eggs upon exposure *hmr-1* RNAi like the *rrf-3* mutant. In contrast, the *ekl-7(vh48)* allele did not show a significant difference in RNAi sensitivity compared to the wild-type strain.

Conclusions: These results suggest that the *vh20* missense allele may uniquely disrupt *ekl-7* function to enhance RNAi sensitivity. Alternatively, *ekl-7(vh20)* could be linked to a background mutation responsible for the Eri phenotype. If expression of EKL-7 E422K causes an Eri phenotype, then double RNAi knockdowns of *hmr-1* and *ekl-7* would be predicted to suppress the Eri phenotype of *ekl-7(vh20)*. Further tests of the *ekl-7* mutations with RNAi targeting additional genes will be necessary to distinguish whether *ekl-7* is an enhancer of RNAi versus an enhancer of *hmr-1*.

Source of Funding: This study was funded by NSERC.

Program MeDiC

PI Christian E. Rocheleau

15-46 - Investigating Herpes Virus U14 Protein as a Modulator of p53 Stability

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Over 20% of human cancers are linked to infectious agents, which produce proteins that modulate tumourigeneses by targeting critical pathways like p53, the most commonly mutated gene in all cancers, and driver of Li-Fraumeni Syndrome (LFS). Using the evilORFeome, a library of 5,300 microbial genes, we conducted a fluorescence-based p53 stability reporter (p53-mClover-P2A-mRFP) screen and identified the U14 protein of human herpesvirus as a modulator of p53 stability and transcriptional activities. U14 stabilised both wild-type and LFS-associated mutant p53 while impairing its transcriptional activity, evidenced by reduced p21 expression and attenuated G1/S cell cycle arrest in U14-expressing cells.

Structural analysis using AlphaFold predicted specific binding of U14 to p53's DNA-binding domain at residue R175. Generation and analysis of a catalytically inactive U14 mutant (I124R, L15R) confirmed the functional importance of this interaction, as the mutant lost the ability to suppress p53 transcriptional activity. Physical association between U14 and wild-type p53 was further validated by co-immunoprecipitation experiments.

These findings implicate U14 in infection-associated oncogenesis, particularly for LFS patients with compromised p53 function. As a nursing student, this project trained me in molecular techniques while highlighting how microbial oncology insights can guide patient education—specifically, advocating for infection monitoring in LFS families to mitigate cancer risks. The work bridges mechanistic discovery with preventive care strategies for high-risk populations.

Program CRP

PI Sampath Loganathan/ YiQing Lu

7 - Lipid Metabolism as a Therapeutic Target in Esophageal Adenocarcinoma: An Exploratory Study

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Introduction: Esophageal adenocarcinoma (EAC) remains one of the most lethal malignancies worldwide, with a 5-year overall survival rate below 20%. Despite the current standard of care involving perioperative chemotherapy with FLOT (5-fluorouracil, leucovorin, oxaliplatin, docetaxel) with or without concomitant radiotherapy, treatment efficacy is limited due to the high frequency of chemoresistance. Lipid metabolism (LM) reprogramming is a hallmark of cancer and supports tumor growth by providing alternative energy sources. Tumor cells rely on increased lipid uptake, transport, and utilization. This study explores the poorly understood role of LM in EAC, aiming to identify metabolic vulnerabilities and LM pathways for potential therapeutic intervention and personalized treatment strategies.

Material and Methods: Tumor and matched normal tissues from patients with locally advanced esophageal adenocarcinoma (EAC) were collected at different treatment stages through biopsy or surgery, with informed consent. A subset of patients underwent surgical resection without receiving neoadjuvant FLOT. Clinical data, including treatment response, were retrieved from medical records. The majority of the fresh tissue samples were processed as input for single-cell RNA sequencing (scRNA-seq). A smaller portion was allocated for establishing live biobanks, including organoids, tumor-infiltrating lymphocytes (TILs), fibroblasts, and murine xenograft models. scRNA-seq analysis assessed both patient-specific and shared cellular compositions. Given that adenocarcinomas originate from epithelial tissue, epithelial cells were isolated for pseudo-bulk RNA-seq analysis, examining the expression profiles of over 30,000 genes. Z-score heatmaps were generated in Python to highlight changes in expression of selected LM-associated receptors and transporter genes in tumor *versus* normal samples. Statistical significance of these genes across treatment time points was also evaluated. To contextualize our findings, gene expression trends observed in our patient cohort were compared with publicly available cancer datasets from cBioPortal. Studies are ongoing to evaluate the efficacy of pharmacological inhibitors targeting selected LM-related genes using CellTiter-Glo viability assays on organoid models.

Results: Z-score-based heatmaps revealed altered expression of several lipid metabolism (LM)-associated genes in tumor samples, including solute carrier (SLC) and fatty acid-binding protein (FABP) family genes. Among these, FABP2 and SLC7A11 were of particular interest in this study. FABP2 expression was significantly lower in the post-treatment tumor/epithelial cell population of chemo-sensitive patients compared to chemo-resistant patients. SLC7A11 expression was highly variable across specimens, with significantly elevated levels in chemosensitive patients, despite its known function in supporting redox balance and promoting metastasis. These findings suggest a need for further investigation, particularly to assess recurrence risk in SLC7A11-high chemo-sensitive EAC patients. We also identified pharmacological inhibitors targeting SLC7A11 and FABPs and have initiated preliminary assessments of their cytotoxic effects on organoids. Finally, CD36, a well-documented fatty acid translocase, was poorly expressed in tumor patients, which is in accordance with the literature data, as EAC is known to be independent of CD36's role in lipid uptake, unlike other cancer types.

Conclusions: This study identifies FABP2 and SLC7A11 as potential biomarkers and therapeutic targets for EAC, emphasizing the need for further research into lipid metabolism's role in tumor progression and the development of personalized, more effective treatments for esophageal adenocarcinoma.

Program CRP

PI Dr. Lorenzo Ferri

10-14 - The associations between child diet and parental stimulation on early childhood development in Ghana

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Background: Globally, millions of children face sub-optimal development due to risk factors such as poor diet and inadequate caregiver stimulation. One hypothesized pathway suggests that improved nutrition leads to better growth outcomes, which in turn elicits more stimulation from parents, ultimately promoting child development. This study explores this hypothesis by examining whether parental stimulation could mediate the association between child dietary diversity and early childhood development in young Ghanaian children.

Methods: This secondary analysis used data from the Mental Health in Ghana study (MHIG) - a cross-sectional survey of households in the Greater Accra Region of southern Ghana. We analyzed a subsample of 460 households including at least one child aged 6-36 months living with both parents. Child diet was measured as the number of food groups (grains/roots/tubers, meat/fish, vitamin A-rich fruits and vegetables, legumes and nuts, eggs, dairy, other fruits and vegetables) reflected in a child's diet in the past 24 hours and operationalized as dietary diversity score (DDS, range 0-7). Caregiver stimulation was reported by both mothers and fathers using the Early Learning Index (ELI). It represents caregivers' engagement in stimulation activities (reading a book or looking at pictures, taking the child out to visit family etc., telling stories, singing, playing, and talking to the child while being busy with housework) in the past 24 hours (range 0-6). Child development was assessed using the Caregiver Reported Early Development Instruments (CREDI) that capture child developmental milestones and behaviours in overall development. Multiple linear regression models were used to examine associations and adjusted for relevant confounders, with analyses stratified by age groups (6-23 months and 24-36 months).

Results: Older children had lower mean z-scores for overall development (-0.40 [1.10]) compared to the reference population, while younger children (0.00 [1.37]) showed development similar to the reference group. The average DDS was higher in older children (3.73 [1.17]) compared to younger children (3.0 [1.52]). Likewise, paternal engagement in stimulating activities was slightly higher in older children (1.85 [1.59]) compared to younger children (1.79 [1.57]). In contrast, maternal engagement in stimulating activities was somewhat greater in younger children (2.97 [1.35]) compared to older children (2.69 [1.51]). No significant association were found between child dietary diversity and parental stimulation in either age group. However, maternal stimulation was positively associated with better overall development in both groups (0.13 SD [95% CI: 0.01, 0.24] for 6-23 months; 0.15 SD [95% CI: 0.03, 0.27] for 24-36 months). Dietary diversity was also linked to better developmental outcomes in younger children (0.11 SD [95% CI: 0.01, 0.22]), but not in older children. Paternal stimulation showed no significant relationship with either child dietary diversity or overall development.

Conclusion: Child dietary diversity was associated with improved development, although this relationship was not explained by parental stimulation. Interventions promoting both dietary diversity and maternal stimulation may be promising for supporting early child development. Further longitudinal and experimental studies are needed to clarify the temporal relationships and explore causal pathways.

Source of funding: The MHIG study was funded by an Early Career Award from the Thrasher Research Fund.

Program CHHD

PI Dr Marilyn Ahun

14-40 - Investigating the Role of CysLT1 in Nrf2 Activation in Lung Macrophages After Chlorine Inhalation

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Background:

Inhalation of chlorine gas, a common industrial and environmental hazard, induces oxidative stress and airway inflammation, necessitating effective cellular defense mechanisms. Neutrophilic inflammation drives the key protective pathway involving the transcription factor Nrf2 that is activated and translocates to the nucleus where it interacts with the antioxidant response element on DNA, leading to the transcription of many antioxidant genes, including NQO1 and HO-1. Recent evidence suggests that the cysteinyl leukotriene receptor 1 (CysLT1) plays a role in mediating Nrf2 activation in airway epithelial cells.³ We hypothesize that macrophages, like epithelial cells, have impaired Nrf2-dependent antioxidant responses following chlorine exposure in mice lacking the absence of CysLT1. To test this, we will expose wild-type (WT) and CysLT1-deficient mice to chlorine gas and will analyze antioxidant responses in lung macrophage responses 24 hours later. Our goal is to determine whether the absence of CysLT1 impairs Nrf2 translocation and downstream antioxidant gene expression in macrophages, revealing a new mechanism of oxidative stress susceptibility.

Methods:

We will use immunofluorescence staining and microscopy to assess Nrf2 translocation, quantitative RT-PCR to measure antioxidant gene expression, and bronchoalveolar lavage (BAL) processing to isolate macrophages from chlorine-exposed wild-type and CysLT1-deficient mice.

Anticipated results:

We expect to observe Nrf2 nuclear translocation in macrophages from wild-type mice after chlorine exposure but not in CysLT1-deficient mice. Expression of Nrf2-dependent antioxidant genes such as NQO1 and HO-1 is anticipated to be elevated in wild-type but reduced in CysLT1-deficient macrophages. These results would suggest that CysLT1 signaling is necessary for initiating the antioxidant response in macrophages following oxidative stress.

Conclusions:

This study will clarify whether CysLT1 signaling is essential for macrophage antioxidant responses following chlorine-induced oxidative stress. By identifying a potential mechanism linking leukotriene signaling to Nrf2 activation, these findings could support the development of targeted therapies to enhance immune cell resilience in chemical inhalation injuries and other oxidative lung conditions.

Source of Funding:

Funded by Canadian Institute of Health Research (CIHR) to Dr. James Martin.

References:

3. McGovern T;Goldberger M;Chen M;Allard B;Hamamoto Y;Kanaoka Y;Austen KF;Powell WS;Martin JG; (n.d.). *Cyslt1 receptor is protective against oxidative stress in a model of irritant-induced asthma*. Journal of immunology (Baltimore, Md. : 1950). <https://pubmed.ncbi.nlm.nih.gov/27226094/>

Program RESP

PI James Martin

4 - Comparative genomics of carbapenemase-producing *Enterobacterales* strains for healthcare-associated infections

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Introduction: Healthcare-Associated Infections (HAI) are among the most common and preventable adverse events in acute care hospitals, posing significant risk to patients. Many HAIs are caused by antimicrobial resistant (AMR) bacteria, such as carbapenem-resistant *Enterobacterales* (CPE). AMR HAIs emerge by two main mechanisms: 1) the acquisition of beneficial mutations that confer resistance to bacteria and which subsequently pass these genes to their offspring, and 2) the acquisition and transfer of specific resistance-encoding genes via mobile genetic elements (such as plasmids) through a process called horizontal gene transfer (HGT). This study investigates within-patient strain-level diversity in CPE infections and aims to identify genetic factors of AMR.

Material and methods:

Ten clinical isolates were obtained from a tertiary care hospital in Montreal, collected from five patients, each of whom had been diagnosed with two temporally distinct AMR bacterial infections during their hospital stay. Genomic DNA was extracted and purified from each isolate and sequenced using long-read whole-genome sequencing. Genome assemblies were performed using Flye and PlasmidSPAdes for the detection of plasmids. Comparative genomic analyses will be used to characterize and differentiate each pair of isolates, determining what defines each isolate as a distinct strain.

Results:

Genomic DNA was successfully extracted and purified for all samples, reaching a minimum concentration of 20 ng/μL, suitable for long-read sequencing. The raw fastq files from the sequencing of the ten isolates were used to generate assemblies of the genome and the plasmids. PCR analysis confirmed the presence of carbapenem resistance genes in all samples. Early genomic comparisons indicate structural differences between isolate pairs from the same patient, suggesting potential gain or loss of resistant elements over time. Ongoing analyses will focus on identifying additional resistance elements and resolve genetic sequences to species and/or strain level.

Conclusion:

This study will contribute to a better understanding of the genomic mechanisms driving strain divergence and resistance evolution in CPE infections in a tertiary care centre.

Source of funding: This research is supported by funding provided by the Canadian Institutes of Health Research (CIHR).

Program RESP

PI Dao Nguyen

3-21 - Occurrence of Intermittent Hypoxemia and Bradycardia in Neonates Prior to Discharge from the Neonatal Intensive Care Unit

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Background: Premature infants in the neonatal intensive care unit (NICU) often experience unstable breathing patterns, including occurrences of apneas, bradycardias, and desaturations or intermittent hypoxemia, collectively described as cardiorespiratory events. Notably, intermittent hypoxemia refers to episodes of low oxygen saturation (<90%), and bradycardia relates to events of low heart rate (<100 bpm in neonates). These events can harm the healthy development of neonates and act as a significant cause of reintubation, extended hospital stays, and higher medical costs. Despite their impact, no standardized definition for cardiorespiratory events or clear guidelines for monitoring them exist. In practice, preterm infants are often discharged if no significant respiratory events are observed over a 5 to 10-day period. However, these decisions are based on limited nurse and physician notes, leading to inconsistencies and may ultimately cause unjustified prolonged hospitalizations. Yet, while bedside monitors capture real-time data, this information is rarely analyzed, discarding valuable data in assessing cardiorespiratory burden objectively. Thus, this study aims to characterize the patterns of cardiorespiratory events, focusing on intermittent hypoxemia and bradycardia, by linking clinical data from electronic medical records and physiological data from bedside monitors to better establish discharge readiness profiles of preterm infants.

Methods: This retrospective study will include infants discharged from the Montreal Children's Hospital NICU between February 1st, 2024, and February 28th, 2025, excluding those with significant congenital anomalies, transferred to other units, or discharged on respiratory support. Data will be collected from electronic medical records, including demographic and peri-discharge information during the 7 days before discharge, including postmenstrual age, daily respiratory support, feeding regimen, and detailed nurse-recorded respiratory events. Bedside monitor data will be extracted by a research data analyst and exported to a CSV file for analysis in MATLAB. Oxygen saturation (SpO₂), heart rate (HR) and respiratory rate (RR) will be evaluated to determine the number of intermittent hypoxemia (SpO₂ < 90 %) and bradycardia (HR < 100), as well as the duration of each of these events and percent time spent below pre-determined thresholds. Normative graphs will be constructed to visualize the pattern of intermittent hypoxemias as a function of gestational age and postmenstrual age at discharge.

Results: After preliminary screening, 250 patients out of 695 were retained for analysis. Data extraction and analysis are ongoing.

Conclusions: We hypothesize that infants across all gestational ages will continue to have intermittent hypoxemia and bradycardia events throughout the days preceding discharge. The results generated from this pilot study will serve as the foundation for future research on the use of biomedical signals. This will allow for the standardization of the requirements to determine discharge readiness in preterm neonates, shortening hospital stays and reducing medical costs.

Source of funding: This project is possible thanks to the Dr. N. Paul Rosman McGill Medical Student Research Bursary, and to Dr. Shalish's team, the Smart Hospital Project, which is funded by the Montreal Children's Hospital Foundation, the Research Institute at the McGill University Health Center, the Fonds de Recherche Quebec Sante, and the McGill Innovation Fund at McGill University.

Program CHHD

PI Dr. Wissam Shalish

6-40 - Sex-Specific Causal Effects of Plasma Proteins on Aortic Stenosis: A Mendelian Randomization Study

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Sex-Specific Causal Effects of Plasma Proteins on Aortic Stenosis: A Mendelian Randomization Study

Background

Aortic stenosis (AS) is a common heart valve disease, affecting approximately 5% of adults aged over 65. The disease often progresses to heart failure or death. Men with AS tend to have greater valve calcification, whereas women more commonly present with fibrosis. These differences suggest the involvement of sex-specific disease mechanisms. Recent studies have identified several circulating plasma proteins, such as LPA, PCSK9, and IL6R, that may causally increase the risk of AS. However, no study has systematically investigated whether these protein-AS relationships differ between males and females. To address this gap, we performed sex-stratified Mendelian Randomization (MR) to evaluate whether the causal effects of plasma proteins on AS risk vary by sex.

Methods

We conducted a two-sample Mendelian randomization (MR) analysis to investigate the causal effects of plasma proteins on aortic stenosis (AS) in a sex-stratified framework. Summary statistics were obtained from two publicly available cohorts: the UK Biobank (n = 48,017; females = 25,904, males = 22,113) for SNP-plasma protein associations, and the International Aortic Valve Genetics Consortium (IAVGC, n = 2,207,845; females = 1,035,430, males = 1,172,415) for SNP-AS associations.

To evaluate sex-specific effects, both datasets were stratified by sex prior to analysis. We first conducted genome-wide association analyses separately for each sex to identify SNPs associated with plasma protein levels in the UK Biobank and SNPs associated with AS in the IAVGC cohort. Instrumental variables were then selected from the SNP-protein associations and matched to corresponding SNP-AS associations within the same sex group.

MR analyses were performed independently in females and males. To evaluate sex-specific differences, we performed formal heterogeneity tests comparing effect estimates between females and males. Additionally, we compared our sex-specific MR results with previous combined-sex MR findings to explore the value of sex-stratification.

Results

After instrumental variable selection, 829 proteins remained eligible for sex-stratified MR analysis. Among these, 817 proteins showed no significant association with aortic stenosis in either sex, while 8 proteins were significantly associated with AS in males only, 3 in females only, and 1 protein, LPA, in both sexes.

In heterogeneity testing, we found that TIMP4 exhibited statistically significant heterogeneity between sexes, showing a protective effect in males but no significant effect in females.

When comparing these findings with the results from combined-sex MR analysis, we found 7 proteins, such as SV2A, TIMP4, and APOH, were only detectable after sex stratification and did not reach significance in the combined analysis. In contrast, 5 proteins including LGALS1, FBN2, and APCS appeared significant in the combined-sex MR, but the observed casualties were actually driven by one sex predominantly. These findings highlight that sex-stratified analysis can reveal meaningful causal relationships that may be overlooked or misinterpreted when sexes are analyzed together.

Conclusions

This study underscores the importance of incorporating sex as a biological variable in studies of cardiovascular diseases. Our findings reveal protein biomarkers with sex-specific effects on AS risk, providing valuable insights for precision medicine and sex-aware therapeutic development.

Program CHAL

PI James C. Engert

7-41 - Machine Learning Models for Luminance and Contrast-Defined Boundaries

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Background:

Boundary detection and differentiation are essential components of visual processing, enabling tasks such as object identification and texture segmentation. To better understand these mechanisms, it is important to examine how different spatial regions surrounding a boundary contribute to its perception.

Methods:

Luminance-modulated boundary stimuli were created across ten contrast levels, with constant Gaussian noise and an evenly sized border. Contrast-modulated boundary stimuli, composed of randomly placed Gabor micropatterns at six modulation levels, were generated using a similar procedure. A simulated observer was assigned two tasks: a detection task, determining whether a vertical boundary was present in a stimulus, and a classification task to distinguish whether stimuli contained a vertical or horizontal boundary. In the detection task, a decision threshold was applied to form the basis of the observer's response. For the classification task, the axis with the greater difference in RMS contrast was selected. The resulting data was analyzed using a machine-learning model, which produced training curves and weight maps.

Results:

The fitted models successfully predicted observer responses and estimated underlying parameter values. This was reflected in the learning curves, which demonstrated high accuracy and low loss across contrast levels. The weight maps for detection tasks had pronounced vertical midlines, dividing light and dark regions, indicating sensitivity to luminance and contrast transitions. Horizontal and vertical weight maps for the classification tasks exhibited quadrant patterns consistent with expected boundary orientations.

Conclusions:

The current model architecture is adaptable and can be extended to more complex stimuli, such as natural textures. Early-stage filter weights may also be learned using a bank of Gabor micropatterns that vary systematically in orientation, frequency, and phase. Collectively, these findings would offer insight into how machine learning can be implemented to decode perceptual decision-making strategies.

Source of Funding:

Funding for this project was provided through Dr. Curtis Baker's grant from the Natural Sciences and Engineering Research Council of Canada (RGPIN-2017-05292).

Program BRaIN

PI Dr. Curtis Baker

4-22 - Baseline circulating tumor DNA as a predictor of clinicopathological features in colorectal cancer

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Introduction:

Colorectal cancer (CRC) remains a significant global health concern, ranking as a top diagnosed cancer and a leading cause of cancer-related death in both men and women. While CRC patients are typically managed based on cancer stage, this approach does not adequately account for individual variations in tumor biology or treatment response, and few diagnostic methods exist to track response and treatment efficacy. Among diagnostic methods, the liquid biopsy (LB) is a minimally invasive test that detects tumor-derived biomarkers in body fluids, enabling real-time monitoring of cancer treatment, response, and recurrence. Carcinoembryonic antigen (CEA) is commonly used as a blood-based biomarker, but its sensitivity and specificity are suboptimal. Circulating tumor DNA (ctDNA), derived from tumor cells and detectable via LB, offers a sensitive, minimally invasive, personalized approach to cancer monitoring. We hypothesize that ctDNA at baseline is associated with clinicopathological characteristics and predicts treatment response and outcome in CRC.

Methods:

A total of 40 CRC patients (pts) with stage I-IV disease were prospectively enrolled in the study. A volume of 3x10ml was obtained for each blood sample using Streck tubes (containing DNA preservative) at baseline from all pts. Cell-free DNA (cfDNA) from these samples was extracted using 4 mL of plasma using magnetic beads in the Qiagen EZ2 machine (QIAGEN). A tumor-informed approach was taken; based on the results of next-generation sequencing using a 51-gene panel on tumor tissue, a targeted digital droplet (dd) PCR assay was designed. TapeStation was used to assess the sample quality; plasma samples with less than 55% cfDNA content were excluded from ddPCR analysis. The ddPCR to detect patient-specific mutations was performed on Bio-Rad systems using specific nucleic acid probes and primers, and the results were evaluated using QX Manager software.

Results:

In mutation-positive patients, ctDNA was detected in 65% of cases (26/40 pts), with detection rates increasing by stage. Mean ctDNA and CEA levels both rose with advancing disease, showing a positive correlation with tumor stage and suggesting their potential as biomarkers of tumor burden and progression.

Conclusions:

Liquid biopsy has a strong and promising potential for the future, being a non-invasive biomarker and a way to detect and track cancer progression. Baseline ctDNA levels were low in early-stage CRC and progressively higher in advanced stages, reflecting increasing tumor burden with disease stage. Future investigations should evaluate the combined use of ctDNA and biomarkers such as CEA, alongside RECIST-based imaging criteria, to further enhance treatment efficacy and accuracy, enabling a more precise detection of minimal residual disease and improving early identification of recurrence.

Program CRP

PI Julia Burnier

8-54 - Modeling the impact of IPEX-associated FOXP3 mutations on Treg ontogeny using artificial thymic organoids

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Introduction: Immune tolerance is essential for preventing self-damage while maintaining host defence. FOXP3⁺ regulatory T (T_{reg}) cells are gatekeepers of immune tolerance and represent a major therapeutic target for the treatment and prevention of autoimmune diseases. A developmental, homeostatic, or functional deficiency in T_{reg} cells triggers a broad spectrum of autoimmune disorders, including Tregopathies. The hallmark Tregopathy is Immune dysregulation, Polyendocrinopathy, Enteropathy, X-linked (IPEX) syndrome, an early-onset multi-organ autoimmune disorder caused by germline mutations in FOXP3, the lineage-defining transcription factor of T_{reg} cells. Clinical observations can include severe enteropathy, chronic dermatitis, and type I diabetes mellitus; without proper treatment, IPEX can be fatal in early childhood. No single mutation defines IPEX; rather, numerous mutations have been identified. Each mutation uniquely impacts the FOXP3 transcriptional program by either restricting DNA binding or abolishing key protein-protein interactions. While the impact of IPEX mutations on T_{reg} function have been described, their role in T_{reg} development remains uncharacterized.

To study human T_{reg} ontogeny, our group has previously developed artificial thymic organoids (ATOs), 3D *in vitro* donor blood-derived cultures that mimic the thymus as a site of T cell development. ATOs mimic T_{reg} cell development by maturing seeded hematopoietic stem cells (HSCs) into developing thymocytes, to then generate thymic T_{reg} cells. We hypothesize that individual mutations selectively impact key aspects of the FOXP3 transcriptional program in T_{reg} development. To investigate this possible association, we aim to leverage high-precision genome editing to generate ATOs harbouring IPEX mutations and ultimately model the course of abrogated T_{reg} development in the thymus.

Experimental plan and methods: We will first generate induced pluripotent stem cells (iPSCs) harbouring IPEX mutations. This will utilize CRISPR prime editing to precisely install single-nucleotide substitutions, enabling the generation of IPEX-associated FOXP3 variants. Prime editing guide RNA (pegRNA) plasmids are first designed and then cloned using Golden Gate Assembly. Once pegRNA constructs are generated, each will be electroporated into iPSCs alongside other prime editing constructs. Electroporated cells will be selected via puromycin selection and fluorescence-activated cell sorting. Sorted iPSCs will be plated as single clones, expanded, and sequenced at the FOXP3 locus to verify editing. Correctly edited iPSC clones will then be differentiated into HSCs, where they will be used to generate IPEX ATOs.

Results: We have demonstrated proof-of-concept differentiation of iPSCs into CD34⁺CD45⁺ HSCs and have characterized the subsequent generation of single-positive CD4⁺ thymocytes from iPSC-derived ATOs. This demonstrates the basis of studying T cell development using iPSC-derived ATOs. Additionally, we have designed and constructed pegRNA cloning plasmids encoding six IPEX-associated FOXP3 mutations: A384T, R347H, R337Q, R397W, R386H, and C424Y.

Conclusions and significance: Modeling the genetics of IPEX in an ATO system will enable us to study how patient-specific genetic differences drive clinical variability among IPEX patients. More broadly, our approach seeks to investigate possible relationships between IPEX syndrome and T_{reg} development.

Sources of funding: This research is supported by the Science Undergraduate Research Award (SURA), made possible through the Faculty of Science and operating funds from the Canadian Institutes of Health Research (CIHR).

Program IDIGH

PI Dr. Ciriaco Piccirillo

2-13 - Estimating population size eligible for lung cancer screening in Nunavik

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BACKGROUND: Inuit in Canada have amongst the highest rates of lung cancer of any population in the world. To reduce deaths through earlier detection, Quebec established a screening program where individuals with a 6-year risk of lung cancer of 2% or higher are eligible for annual CT screening using Tammemagi and colleagues' PLCOm2012 risk model. However, Quebec's program implementation poses obstacles to Nunavimmiut accessing screening. Despite Nunavimmiut facing a high risk of lung cancer, no estimation has been done of the population size eligible for screening in Nunavik. We sought to estimate the number of people eligible for lung cancer screening in Nunavik using the PLCOm2012 model.

METHODS: Data for this study came from the QANUILIRPITAA? 2017 Inuit-led health survey that included people aged 40 and above from all communities in Nunavik. We transformed any survey variables that require different categorizations to match the PLCOm2012 model. Variables included age, education, BMI (kg/m²), diagnosis of COPD/emphysema/chronic bronchitis, personal history of cancer, family history of lung cancer, race/ethnicity, smoking status, average number of cigarettes smoked daily, smoking duration and smoking cessation duration. Personal history of cancer was defined as having had any cancer in their lifetime. Smoking status was classified as either current or former smoker. Former smokers are people who currently don't smoke but smoked at least 100 cigarettes (4 packs) in their life. Current smokers are people who smoke daily or occasionally at the time of the survey. Non-smokers were excluded. Smoking duration was defined as the difference between age at survey and age when the person starts smoking (daily or occasionally). Due to missing data on smoking cessation for former smokers, we used the mean smoking cessation duration for each 5-year age group starting at 40 years old from the previous 2004 survey.

RESULTS: Amongst the 512 participants of the QANUILIRPITAA? 2017, 449 were ever-smokers (77% current smokers, n=347). 96% of the participants were Inuit (433/449). The mean age was 54 years. Mean BMI was 27.7. 75% of the participants did not complete high school (311/412), 25% were diagnosed with COPD/emphysema/chronic bronchitis (83/327) and 7% (27/383) had a history of cancer. Average number of cigarettes smoked was 14 in current smokers (n=306) and 11 in former smokers (n=78).

Both current and former smokers smoked for an average of 17 years (n=299, n=80). Smoking cessation duration was on average 14 years for non-smokers. Family history of lung cancer could not be calculated at this time due to missing data.

CONCLUSION: Identification of eligible Nunavimmiut for lung cancer screening will help better plan the resources needed to create accessible screening pathways in Nunavik. For our next steps, after accounting for the missing variable and imputing missing data, risk estimates of lung cancer for each individual will be calculated using the PLCO12m model. The proportion of individuals whose estimated risk is at least 2% will then be calculated.

SOURCE OF FUNDING: Madeline Yaaka is supported by the RECRU summer studentship award.

Program RESP

PI Dr. Faiz Ahmad Khan

13 - Curing brain cancer with immune cell 'debris' - Characterization of extracellular vesicles derived from lethally irradiated natural killer cells with cytotoxic activity against glioma stem cells

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Background: Glioblastoma multiforme (GBM) is an incurable brain cancer, affecting 4 in 100 000 Canadians. Previously, our group has shown in mice that lethal tumours formed by the mesenchymal subset of GBM-initiating cancer stem cells (GSCs) can be eradicated by addition of intracranial injection of natural killer cells to tumour depopulating chemotherapy. Chemotherapy by itself had (as in patients) no curative potential. Injection of live NK cells is associated with multiple biosafety, logistic and immunocompatibility risks, so alternative approaches are badly needed. We hypothesized that NK cell-derived cellular fragments known as extracellular vesicles (EVs) may carry the killing apparatus of NK cells and thereby serve as an off-the-shelf substitute for chemoimmunotherapy in GBM.

Methods: EVs were isolated from irradiated (5Gy) NK92MI immortalized NK cells or controls by either ultracentrifugation or size exclusion chromatography. The resulting NK-EV preparations were evaluated using nanoparticle tracking analysis (NTA), super-resolution imaging (ONI), transmission electron microscopy (TEM) and Exoview single EV analysis. NK-EVs were further molecularly characterized by western blot for purity (Alix, CD63, CD9, CANX) and functional cargo (Granzyme A/B, Perforin, NKG2D) and while their cytotoxicity was assessed by MTS assay against mesenchymal and proneural GSC targets. The presence of target binding receptor (NKG2D) was further validated by ELISA. Finally, NK-EVs were injected into tumour-bearing Fox Chase SCID mice post chemotherapy, where tumor burden survival was evaluated by bioluminescent imaging and clinical monitoring.

Results: We observed that irradiation increases the content of EVs in cultures of NK92MI cells. TEM and NTA revealed a varied size distribution of irradiated and non-irradiated NK-EVs. NK-EVs from irradiated cells exhibited increased expression of target binding (NKG2D) and killing proteins (perforin) as well as EV markers (Alix). Furthermore, NK-EVs in the MTS functional assay showed a marked increase in GSC cell death, corroborated by an increase in mouse survival rates post immunochemotherapy.

Conclusions: Irradiation of NK cells drives release of NK-EVs with potent cytotoxic activity against GSCs. Further investigation into the mechanism of observed synergy between temozolomide and NK-EVs will provide clarity on their therapeutic potential for GBM treatment.

Sources of Funding: This project is funded by the CIHR and the Charles Bruneau - CIBC Foundation. Instrumentation of the Nanomedicine (CAN) Facility is supported by the Canada Foundation for Innovation grant.

Program CHHD

PI Janusz Rak

13-34 - Variability of CA-125 KELIM Scores Across Racial Backgrounds in Patients Undergoing Neoadjuvant Chemotherapy for High-Grade Serous Ovarian Cancer

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Background: The CA-125 KELIM (meaning CA-125 ELIMination rate constant K) score is a validated mathematical modeling tool that reflects tumor chemosensitivity in patients receiving neoadjuvant chemotherapy (NACT) for high-grade serous ovarian cancer (HGSOC). Higher KELIM values have been associated with favorable prognosis and improved treatment response. However, limited data exist on how these scores may vary across racial backgrounds.

Objective: This study aims to explore whether CA-125 KELIM scores differ among patients of diverse racial backgrounds undergoing NACT, in order to identify potential disparities in tumor chemosensitivity or biological behavior.

Methods: We retrospectively collected and analyzed CA-125 values at baseline, prior to the second, third, and (when available) fourth chemotherapy cycles from anonymized patient data at the McGill University Health Centre (MUHC). KELIM scores were calculated using the Biomarker-Kinetics platform, requiring at least three timepoints within 100 days. Of the initial 91 patients, 67 met the inclusion criteria, receiving NACT at the MUHC and having a known racial background. Patients were categorized by self-reported race. Standardized KELIM scores were classified as favorable (≥ 1.0) or unfavorable (< 1.0) and compared across racial groups.

Results: Preliminary findings revealed variability in KELIM scores by racial background. Of the 67 patients included in the final analysis, 27 (40%) had favorable KELIM scores (≥ 1.0), while 40 (60%) had unfavorable scores (< 1.0). When stratified by racial background, we observed differences in the distribution of tumor chemosensitivity. Among White patients ($n = 15$), 5 (33%) had favorable KELIM scores. In the "Another race category" group ($n = 9$), 2 (22%) were favorable. Middle Eastern patients ($n = 3$) had 2 favorable outcomes (67%), while both Asian and South Asian patients ($n = 2$ each) showed a 50% favorable score rate. Latino and Black patients had limited representation ($n = 1$ and $n = 4$, respectively).

Conclusion: These results suggest that CA-125 KELIM scores may differ across racial groups, which could have implications for personalized treatment approaches and eligibility for clinical trials. However, due to the relatively small cohort size in this study, further research with larger and more diverse populations is needed to validate these trends and to assess whether population-specific KELIM cutoffs are supported.

Program CRP

PI Dr. Reitan Ribeiro

7-47 - Open-source 3D Image Analysis in Python for Mitochondrial Network Analysis

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BACKGROUND: Mitochondria play a central regulatory role in connective tissue biology, such as the metabolic and functional plasticity of mesenchymal stem cells (*MSCs*), the progenitors of connective tissue lineages. Mitochondrial networks, fission, and fusion orchestrate cellular metabolism by modulating energy production pathways to meet bioenergetic demands during differentiation. Furthermore, mitochondrial-derived ATP and reactive oxygen species regulate extracellular matrix (*ECM*) deposition by activating and modulating collagen synthesis pathways. Thus, mitochondrial dynamics integrate metabolic adaptation, lineage specification, and ECM remodeling, ensuring tissue homeostasis and repair in connective tissues. This is crucial to further understanding connective tissue biology and pathophysiology and developing efficient therapies and tissue engineering applications. In this study, we aim to develop a robust open-source automated 3D image analysis pipeline for subcellular organelle-level analysis of mitochondrial network organization.

METHODS: Mitochondria in bone marrow-derived *MSCs* were stained using MitoTrackerTM Red dye following the manufacturer's protocol and imaged using a Zeiss LSM780 confocal microscope. 3D fluorescent confocal z-stack image analysis was performed exclusively in Python using the BioIO, scikit-image, Skan, and napari libraries. Gaussian filtering and Laplacian transform (LoG) were used for pre-processing, producing smooth and denoised images with enhanced features. Global Otsu thresholding was applied before thinning and analyzing with Skan to measure the lengths of skeletonized features.

RESULTS: LoG processing appears to be highly effective at accentuating mitochondrial features from background signal and cellular autofluorescence while sufficiently isolating features such that global Otsu is indistinguishable from adaptive thresholding. Pixel length measurements are automatically converted into physical length scales using image metadata for straightforward data interpretation.

CONCLUSIONS: We have developed a simple workflow for 3D image analysis of mitochondrial network analysis in Python. Future work aims to refine the performance and speed of this pipeline, especially for batch processing. A key feature of this workflow is the low computational cost, which enables CPU-based computation and eliminates hardware limits imposed by GPU acceleration. Future distribution will implement a GUI and be distributed either locally or remotely, depending on hosting and data security protocols.

SOURCES OF FUNDING: Research is funded by the Réseau de Thérapie Cellulaire, Tissulaire et Génique du Québec, the Réseau de Recherche en Santé Buccodentaire et Osseuse, the Fonds de recherche du Québec, and the Natural Sciences and Engineering Council of Canada.

Program SIS

PI Rahul Gawri

16-53 - Trajectories and Determinants of NT-proBNP in the McGill SLE Research Cohort

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Background: Patients with SLE are at increased risk of cardiovascular disease. Previous studies have demonstrated that SLE patients have higher levels of N-terminal prohormone of brain natriuretic peptide (NT-proBNP), a biomarker of cardiac dysfunction, and that higher NT-proBNP levels are associated with cardiovascular damage within this population. However, the longitudinal progression of NT-proBNP in SLE has not yet been investigated. We examined the trajectories of NT-proBNP and explored cross-sectional associations with demographic and disease characteristics.

Methods: This study analyzed data from the McGill SLE research cohort, which serially enrolls patients presenting for clinical care. Labs and clinical/demographic data are collected at cohort entry and annually. Serial serum concentrations of NT-proBNP were measured yearly in patients from March 2022 to May 2025. Analyses were conducted to first assess the prevalence of elevated NT-proBNP (above 133 pg/mL) at first assessment, and determine correlations with baseline variables (age, sex, race/ethnicity, age at SLE diagnosis, disease duration, smoking, hypertension, EKG, and organ damage). We then looked at the trajectory of NT-proBNP measurements and classified individuals into the following categories: abnormal at baseline and remained abnormal; abnormal at baseline and normalized; normal at baseline and became abnormal; normal at baseline and remained normal. We compared the baseline variables among individuals across the 4 categories.

Results: We studied 294 patients with two or more levels. At first assessment, 101 (34.4%) of NT-proBNP levels were elevated [mean 243.6, median 91 (interquartile range, IQR 55 - 171.8) pg/mL]. The median age at SLE diagnosis tended to be higher in those with an abnormal baseline NT-proBNP level (31.5 years, IQR 23.7-46.1) versus normal (27.4 years, IQR 20.5-35.5). The median SLE duration was almost twice as long in those with an abnormal baseline level (24.4 years, IQR 16.1-36.3) versus normal (14.8 years, IQR 9.4-22.4). Smoking, having an abnormal EKG, and having organ damage (cardiovascular, renal, and pulmonary) were also associated with a higher baseline NT-proBNP level. Of the 101 patients whose level was initially abnormal, most (79, 78.2% of 101) remained abnormal at the second assessment and the remaining 22 normalized. Of the 193 patients whose level initially was normal, 30 (15.5 % of 193) became abnormal at second assessment. None of the patients with a level ≥ 350 at first assessment normalized to <133 . Longer SLE duration, as well as cardiovascular, pulmonary, and renal damage were associated with persistent NT-proBNP elevation.

Conclusions: Over a third of the people in our multi-ethnic long-term SLE cohort had an initially abnormal NT-proBNP level, and most (78%) of these remained abnormal at the second assessment, while over one-tenth (15.5%) of those with an initially normal value became abnormal at the second assessment. Individuals with abnormal levels tended to have a longer SLE duration and more organ damage. None of the individuals with a level ≥ 350 normalized over the 2-3 years of our evaluation. Future analyses will correlate our findings with ventricular function and valvular abnormalities on echocardiograms.

Program IDIGH

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