ST. MICHAEL'S
UNITY HEALTH TORONTO

Research Training Centre

Research Training Centre

RESEARCH DAY 2025

PROGRAM BOOK

Tuesday, May 27, 2025
8:30 AM – 4:30 PM
LKSKI, B&M Syron Exhibit Hall and
2nd Floor Auditorium

Research Training Centre
RESEARCH DAY 2025

ST. MICHAEL'S
UNITY HEALTH TORONTO
Research Training Centre

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Patricia O'Campo

Keynote Speaker
Mikaela D. Gabriel

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RESEARCH DAY 2025

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PROGRAM SCHEDULE

8:30 AM – 9:10 AM	**Registration-Speakers, Judges, Presenters, Attendees** *Pick up your name tags from the Registration Table.* *All judges and speakers must also check in and pick up their event materials at the Registration Table.*	**LKSKI 2nd Floor B&M Syron Exhibit Hall**
8:30 AM – 9:10 AM	**Breakfast** *Please enjoy a light breakfast after you have picked up your name tag at the Registration Table.*	**LKSKI 2nd Floor Allan Waters Family Auditorium**
9:10 AM – 9:15 AM	**Welcome Remarks** Dr. Patricia O'Campo, PhD, Director, Research Training Centre Ori Rotstein, MD, MSc, FRCSC, Vice President, Research and Innovation	**LKSKI 2nd Floor Allan Waters Family Auditorium**
9:15 AM – 9:20 AM	**Opening: Keynote Speaker Session** *Session Introduction:* Dr. Patricia O'Campo, PhD, Director, Research Training Centre	**LKSKI 2nd Floor Allan Waters Family Auditorium**
9:20 AM – 9:55 AM	**Keynote Speaker Session** **Interview with Dr. Mikaela Gabriel, C. Psych, Italian & Mi'kmaq of Ktaqmkuk** Scientist, MAP & Well Living House, Li Ka Shing Knowledge Institute Assistant Professor, Dalla Lana School of Public Health, U of T Canada Research Chair, Indigenous Women and Two-Spirit Mental Health and Homelessness	**LKSKI 2nd Floor Allan Waters Family Auditorium**
9:55 AM – 10:10 AM	**Coffee Break** *Coffee and snacks provided*	**LKSKI 2nd Floor Allan Waters Family Auditorium**
10:10 AM – 11:40 AM	**Oral Presentations Session I** **Clinical Research/Dry Bench** *Session Introduction & Chair:* Dr. Patricia O'Campo	**LKSKI 2nd Floor Allan Waters Family Auditorium**
11:40 AM – 12:40 PM	**Lunch & Networking** *Lunch provided*	**LKSKI 240 and 241**
11:40 AM – 12:40 PM	**Poster Set-up** *Poster presenters only*	**LKSKI 2nd Floor B&M Syron Exhibit Hall**
12:40 PM – 2:00 PM	**Open Poster Viewing**	**LKSKI 2nd Floor B&M Syron Exhibit Hall**

*LKS 136 is a dedicated quiet room for those looking for a break and space to rest from 12 – 5 pm

PROGRAM SCHEDULE (Cont'd)

12:40 PM – 2:00 PM	**Poster Judging (5 min to present, 3 min for Q&A)** *Poster judges please submit scores online and bring paper copies of rubrics to the Registration Table*	**LKSKI 2nd Floor B&M Syron Exhibit Hall**
2:00 PM – 3:30 PM	**Oral Presentations Session II** **Basic Research/Wet Bench** *Session Introduction & Chair:* Dr. Patricia O'Campo	**LKSKI 2nd Floor Allan Waters Family Auditorium**
3:30 PM – 4:00 PM	**Poster & Oral Competition Deliberation**	**LKSKI 2nd Floor B&M Syron Exhibit Hall**
4:00 PM – 4:30 PM	**Competition Awards & Closing Remarks** *RTC Oral and Poster Presentation Awards* *Closing Remarks & Session Chair:* Dr. Andrea Tricco, PhD, Executive Director, Li Ka Shing Knowledge Institute	**LKSKI 2nd Floor Allan Waters Family Auditorium**
5:00 PM – 7:30 PM	**SRSA Networking Social** *Come celebrate all your hard work after a long Research Day with us at Imperial Pub on Dundas! Open to all Research Day attendees. Free appetizers provided.*	**Imperial Pub on Dundas**

*LKS 136 is a dedicated quiet room for those looking for a break and space to rest from 12 – 5 pm

KEYNOTE SPEAKER

Dr. Mikaela D. Gabriel

(C. Psych, Italian & Mi'kmaq of Ktaqmkuk)

Scientist, MAP & Well Living House, Li Ka Shing Knowledge Institute

Assistant Professor, Dalla Lana School of Public Health
U of T

Canada Research Chair, Indigenous Women and Two-Spirit Mental Health and Homelessness

Dr. Mikaela D. Gabriel (Italian & Mi'kmaq of Ktaqmkuk; she/her) is a clinical and counselling psychologist, professor, and researcher exploring Indigenous health and wellbeing, urban cultural connection, and housing transitions for Indigenous Peoples in Canada. Her primary research focus is the promotion of positive cultural identity, strength, and healing through traditional knowledge and cultural support in housing transitions, experiences of homelessness, and accessing primary care centres. Dr. Gabriel's research and clinical work is grounded in Indigenous cultural approaches to mental health, trauma-centered approaches, with narrative therapeutic strategies. She has provided mental health care across inpatient, outpatient, and community mental health treatment settings, and currently works supporting Indigenous urban mental health treatment in Toronto Dr. Gabriel is a scientist with Well Living House and MAP Centre for Urban Health Solutions in the Li Ka Shing Knowledge Institute of St. Michael's Hospital. She is an assistant professor at the Waakebiness Institute for Indigenous Health at the Dalla Lana School of Public Health/University of Toronto, where she completed a postdoctoral fellowship and continues to teach and support research efforts. She is a writer, traveler, and an auntie.

Research Training Centre
RESEARCH DAY 2025

ST. MICHAEL'S UNITY HEALTH TORONTO
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ORAL PRESENTATIONS

Oral Presentation Session I: 10:10 am – 11:40 am
Oral Presentation Session II: 2:00 pm – 3:30 pm
Location: LKSKI 2nd Floor Allan Waters Family Auditorium

Session I *Clinical Research (Dry Bench) Stream*

Time	Title	Presenter
10:10 am	Canadian inhaler users awareness of climate implications: a national survey	**Stacey Butler, MSc, PhD**
10:25 am	Effective strategies for achieving equity in genetic research: A systematic review	**Charlotte Calvez, MSc (c)**
10:40 am	Choroid Plexus Volume in Pathologically Confirmed Alzheimer's Disease	**Francis Fernandes, MSc (c)**
10:55 am	Sex and red cell transfusion in cardiac surgery: Why are women transfused more often?	**Helen Jiang, MSc (c)**
11:10 am	Acute Respiratory Distress Syndrome Following Spinal Cord Injury: Risk Factors and Impact on Clinical Outcomes in a National Multi-Center Cohort	**Christopher Lozano, MD, MSc (c)**
11:25 am	The use of gender frameworks in cardiometabolic disease and nutrition research: a scoping review	**Seyedehsara Osia, MPH (c)**

Session II *Basic Research (Wet Bench) Stream*

Time	Title	Presenter
2:00 pm	Integrated Breast Tumor and Placenta -on-a-Chip Model to Define the Molecular Profile of Pregnancy-Associated Breast Cancer	**Yasmin Abdelkader, PhD (c)**
2:15 pm	AI-driven Optimization of Lipid Nanoparticles for Fetal Gene Therapies	**Amr Abostait, PhD (c)**
2:30 pm	YAP/TAZ manipulation influences chemotherapy induced IFN signalling in lung cancer	**Sharon Binstock, PhD (c)**
2:45 pm	RhoA is a key mediator of mitochondrial remodeling in Polycystic Kidney Disease via the ROCK/cofilin and formin pathways	**Rohankrishna Harikumar, PhD (c)**
3:00 pm	Lipoprotein(a) and the Arterial Endothelium: Elucidating Mechanisms of Residual Cardiovascular Risk	**Andria Henry, PhD (c)**
3:15 pm	Microglia prevent spontaneous recurrent age-dependent demyelination	**Jonathan Monteiro, PhD (c)**

POSTERS

Poster Session: 12:40 PM – 2:00 PM
Location: LKSKI 2nd Floor B&M Syron Exhibit Hall

Clinical Research (Dry Bench) Stream

Poster #	Abstract Title	Presenter
2	Identifying ultrasound and photoacoustic imaging biomarkers from Mitochondrial Therapies applied to Kidney Transplants	**Alex Chen**
6	Changes in Stress and other Mental Health Outcomes among Syrian Refugee Women from Before to During the COVID-19 Pandemic	**Caitriona Federico**
18	Investigating the efficacy of a single-session psychotherapy for suicide risk in adults	**Onjoli Krywiak**
23	ResearchWaste.info: Raising awareness of avoidable waste in health research	**Pavel Zhelnov**
26	DialySnake: Safety and Efficacy in Removing Intraluminal Fibrin Plugs in Peritoneal Dialysis Catheters	**Ria Khan**
28	Evaluating feasibility of a primary-care milk fat recommendation intervention for young children: An internal pilot randomized trial	**Sabrina Lai**

Poster Session: 12:40 PM – 2:00 PM
Location: LKSKI 2nd Floor B&M Syron Exhibit Hall

Basic Research (Wet Bench) Stream

Poster #	Abstract Title	Presenter
1	Brain myeloid cells regulate oligodendrogenesis and myelination in the developing central nervous system	**Alana Hoffmann**
3	The role of erythropoietin signaling in the liver	**Apu Chowdhury**
4	Deciphering CD47-driven platelet-tumor crosstalk and its associated transcriptomic changes in NSCLC metastasis	**Asa Lau**
5	Monocytes reduce remyelination efficiency	**Bianca Hill**
7	KIFC1 inhibition is a promising therapeutic strategy in lung cancers with centrosome amplification	**Christopher Zhang**
8	The Impact Of Prostaglandin E2 on Fibro-Adipogenic Progenitors	**Christina Doherty**
9	Crosstalk Between Endothelial and Perivascular Stromal Cells: Orchestrating Myofibroblast Activation	**Elham Karimizadeh**
10	Identifying potential mechanisms whereby knocking down YAP in adipocytes improves glucose metabolism	**Fan Yang**
11	Dysfunctional oligodendrocytes accumulate in human cognitive decline	**Georgina Craig**
12	Triglyceride- and Cholesteryl Ester-Rich Lipid Droplets Exhibit Different Effects on Low Density Lipoprotein Transcytosis in Endothelial Cells	**Grace Wen**
13	Vitamin D Mediated Mechanisms in Autoimmune Disease	**Guy Nevo**

14	Differential regional vulnerabilities to age-related myelin pathology in human brain	**Jessica Thapar**
15	Investigating YAP/TAZ-mediated regulation of the spindle assembly checkpoint in lung cancer	**Kangni Zou**
16	Midbrain somatostatin cells stimulate breathing and motor activity in rodents in vivo	**Kayla Baker**
17	Modeling drug tolerance and minimal residual disease to discover effective therapeutic combination strategies for EGFR-mutated lung cancer	**Kristyna Gorospe**
19	The effects of HMGB1 nuclear depletion on the DNA damage response following traumatic brain injury	**Laura Siracusa**
20	The proto-cadherins Dchs1 and FAT4 mediate profibrotic polarization of macrophages in direct contact with fibrogenic fibroblasts	**Li Diao**
21	Placenta-on-a-Chip Reveals How Mechanical Pressure Modulates Barrier Function and Trophoblast Differentiation in Placental Dysfunction	**Mahmoud Abdelkarim**
22	Elucidating the role of CXCL1 and CXCL8 in inflammation-induced keratinocyte migration.	**Neetu Rambharack**
24	The Role of ABO Blood Groups in SARS-CoV-2 Infection	**Priyal Shah**
25	Investigating photoacoustic imaging as a novel, radiation-free method for imaging the injured lung	**Rajiv Sanwal**
27	Investigating oncolytic viruses as a vehicle for delivering CD47 blockade in murine models of lung cancer	**Ryunosuke Hoshi**
29	VEGF-A and autocrine regulator of keratinocyte migration during skin inflammation.	**Vida Maksimoska**
30	A Novel Mechanosensitive Factor Regulating Fibroblast Activation	**Xinying Guo**
31	Novel Mechanism of Immune Suppression: Unveiling the Roles of Platelet Desialylation	**Xun (Grace) Wu**
32	Novel Cancer Therapy: Targeting Integrin β3 PSI Domain to Simultaneously Impede Cancer Metastasis and Cancer-Associated Thrombosis	**Zack Rousseau**
33	Shared Genetic Risk in Autoimmune and Inflammatory Diseases	**Anne Wu**
34	How to keep myofibroblasts under control: culture of mouse skin fibroblasts on soft substrates	**Dong Ok (Donna) Son**
35	Exploring the Association of Neuropsychiatric Symptoms with Blood-Based Biomarkers in Alzheimer's Disease and Mild Cognitive Impairment	**Rahmah Ikhlas**

ABSTRACTS – ORAL PRESENTATIONS

Oral Presentation Session I – Clinical Research (Dry Bench) Stream

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01 Canadian inhaler users awareness of climate implications: a national survey

Dr. Stacey J Butler, PhD, MSc, Division of Respirology, Unity Health Toronto; Dr. Geneviève C. Digby, MD, FRCPC, MSc, Department of Medicine, Queen's University; Caitlin Roy, BSP, ACPR, MSc, Department of Pharmacy Services, Saskatchewan Health Authority; Dr. Sze Man Tse, MD, FRCPC, MPH, Division of Respiratory Medicine, Centre Hospitalier Universitaire Sainte-Justine; Jill Hubick, RN, CRE, Lung Saskatchewan; Carolyn McCoy, RRT, Canadian Society of Respiratory Therapists; Ivy Lam, RPh, Leslie Dan Faculty of Pharmacy, University of Toronto; Dr. Alexander Singer, MD, FRCPC, Department of Family Medicine, University of Manitoba; Eva Leek, RRT, Division of Respirology, Unity Health Toronto; Dr. Sakina Walji, MD, FRCPC, Department of Family Medicine, Sinai Health System; Dr. Valeria Stoynova, MD, FRCPC, Vancouver Coastal Health Research Institute; Dr. Samir Gupta, MD, FRCPC, MSc, Division of Respirology, Unity Health Toronto

Background: People with lung diseases are vulnerable to climate change; yet the most common inhaler device, metered dose inhalers (MDIs), have a high carbon footprint and contribute to climate change.

Aim: We sought to understand the perspectives of inhaler users in Canada on climate change, current inhaler disposal practices, and awareness of inhaler climate implications.

Methods: Canadians (aged ≥ 16 years) who reported using an inhaler in the previous 6 months were invited via non-profit/charitable or patient advocacy organizations newsletters to complete a cross-sectional online survey (November 2024 – February 2025). Multivariate regression models assessed the association between sociodemographic factors and climate change risk perception index scores, inhaler disposal methods, awareness of inhaler climate impacts, and willingness of MDI users to switch to low carbon footprint devices.

Results: There were 255 respondents (mean age 68 ± 12 years, 64% female, 80% MDI users). Most individuals were concerned about climate change (84%) but only 20% were aware that MDIs have high carbon footprints. Older individuals and women were less likely to be aware of the carbon footprint of MDIs, while higher education was associated with greater awareness ($p < 0.05$). People who already experienced health changes due to climate events (31%) had higher climate change risk perception scores ($p < 0.001$). Most respondents reported disposing of their inhalers in garbage bins (58%) and when provincial pharmacy return programs were available (n=216) they were underutilized (26%). Nearly all MDI users (92%) were willing to switch to a lower carbon footprint device.

Conclusions: Inhaler users are concerned about climate change but lack awareness of inhaler climate impacts. Interventions that promote education and awareness, as well as promote the use of low carbon devices, and sustainable disposal practices could reduce inhaler-related climate impacts.

Funding: Choosing Wisely Canada

ABSTRACTS – ORAL PRESENTATIONS

Oral Presentation Session I – Clinical Research (Dry Bench) Stream

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02 Effective strategies for achieving equity in genetic research: A systematic review

Charlotte Calvez, MSc, Institute of Health Policy and Management, University of Toronto; Arielle Nsenga, Department of Biochemistry and Population Health, University of Toronto; Vernie Aguda, MSc, Trillium Health Partners; Rushil Dua, St. Michael's Hospital, Unity Health Toronto; Yvonne Bombard, PhD, Institute of Health Policy and Management, University of Toronto

Introduction: The lack of diversity in genetic research is well-documented. Significantly fewer studies are conducted with racialized populations, and current data does not represent these populations. This reality directly impacts the quality of genetic research by limiting discoveries and the generalizability of evidence. It also exacerbates existing health inequities, as a lack of diversity in research can hamper proper diagnosis and treatment. Despite the clear need for greater diversity in genetic research, no studies have reviewed strategies to address it.

Aim: This systematic review aims to synthesize and evaluate the effectiveness of existing equity-focused strategies for conducting genetic research with underrepresented populations.

Methodology: A search was conducted using Medline, EMBASE, PsychInfo, Google Scholar, citation searching and Cochrane databases. Articles were deemed eligible if they focused on evaluating a genetic research strategy in underrepresented populations. Data extraction is focused on outcomes related to effectiveness. The quality of the evidence will be assessed using standardized tools. Two independent reviewers are performing all review process steps. Data will be synthesized through narrative synthesis, frequency data for outcomes, and thematic analysis.

Results: The search returned 2486 articles. To date, 31 articles have proceeded to data extraction. Most of these studies are based in the United States (N=28) and target African American populations (N=15). Additionally, most strategies focus on recruiting via different mediums (e.g., email, mail, or phone) or locations (e.g., community, hospital, or clinic).

Conclusion: This systematic review will serve as a resource for understanding current gaps in equity-oriented genetic research. Preliminary findings show few strategies focus on design, data collection, and reporting, as most studies evaluate recruitment. Additionally, not all underserved populations are equally represented in these strategies. The results of this study are vital for identifying research gaps and serve as a valuable resource for researchers conducting genetic research with underrepresented populations.

ABSTRACTS – ORAL PRESENTATIONS

Oral Presentation Session I – Clinical Research (Dry Bench) Stream

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03

Choroid Plexus Volume in Pathologically Confirmed Alzheimer's Disease

Francis Fernandes BSc, Graduate Student, Keenan Research Centre for Biomedical Science, Li Ka Shing Knowledge Institute, St. Michael's Hospital & Institute of Medical Sciences, University of Toronto; Marc Khoury MSc, Graduate Student, Keenan Research Centre for Biomedical Science, Li Ka Shing Knowledge Institute, St. Michael's Hospital;Adrienne L. Atayde MSc, Research Staff, Keenan Research Centre for Biomedical Science, Li Ka Shing Knowledge Institute, St. Michael's Hospital; Avyarthana Dey PhD, Postdoctoral Fellow, Neurosciences Research Program, Keenan Research Centre for Biomedical Science, Li Ka Shing Knowledge Institute, St. Michael's Hospital; Andy Z. Ma BSc, Undergraduate Student, Computer Sciences Co-op Program – Faculty of Arts & Science, University of Toronto; Felix Menze MSc, Graduate (Doctoral) Student, Sunnybrook Health Sciences Centre, Sunnybrook Research Institute & Department of Medical Biophysics, University of Toronto; Nathan W. Churchill PhD, Scientist, Keenan Research Centre for Biomedical Science, Li Ka Shing Knowledge Institute, St. Michael's Hospital & Department of Physics, Toronto Metropolitan University

Background: The choroid plexus (CP), located in the brain's lateral ventricles, plays a vital role in brain homeostasis by clearing cellular/molecular waste. Alzheimer's disease (AD) progression is associated with accumulation of toxic byproducts (hyperphosphorylated Tau & amyloid-beta) due to impaired cellular/molecular clearance. CP involvement in the clearance of these pathological byproducts is yet to be elucidated – thus being of substantial clinical interest. We examined CP volume, as a marker of function, in pathologically-confirmed AD and hypothesized that CP-Volume increases with greater AD-pathology, suggesting impaired functioning.

Methods: Structural T1-weighted magnetic resonance imaging (sMRI) from 312 patients with pathological workup were analyzed from the National Alzheimer's Consortium Centre dataset. Patients were grouped based on pathological staging of accumulated tau (Thal staging) and amyloid (Braak staging): Normal (Thal 0-2, Braak 0-2), Pre-AD (Thal 1-5, Braak 0-2), Mild-AD (Thal 1-5, Braak 3-4), & Severe-AD (Thal 1-5, Braak 5-6). sMRI underwent automatic segmentation followed by estimation of bilateral CP-Volumes normalized to estimated total intracranial volume. Bayesian multilevel regression was performed by modelling normalized CP-Volume as a function of pathological status, controlling for age, sex and time between sMRI acquisition and death. Group differences in CP-Volume were reported in terms of median effect and 90% Highest Density interval (HDI), contrasting between normal and path-confirmed groups.

Results: There was a high probability (>0.9) of greater CP-Volume in the path-confirmed AD groups compared to normal. The magnitude of effect increased with pathological burden, with mild (1.78×10^{-4} cm3, [7.11×10^{-5}, 2.84×10^{-4}]) and severe-AD (1.75×10^{-4} cm3, [9.77×10^{-5}, 2.55×10^{-4}]) having the largest effect.

Conclusions: Considering evidence that impaired clearance (and by extension the CP) is related to AD-pathology, our findings suggest we can detect morphological changes (via CP-Volume changes) related to these processes and supports the feasibility of sMRI in assessing CP as a correlate of pathological burden.

ABSTRACTS – ORAL PRESENTATIONS

Oral Presentation Session I – Clinical Research (Dry Bench) Stream

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04 Sex and red cell transfusion in cardiac surgery: Why are women transfused more often?

Helen Jiang, BMSc, Department of Physiology, University of Toronto; Kyle Chin, MSc, Department of Anesthesia, St. Michael's Hospital; Nadine Shehata, MD, MSc, Department of Laboratory Medicine & Pathobiology, University of Toronto; Gregory Hare, MD, PhD, Department of Physiology, University of Toronto; C David Mazer, MD, Department of Physiology, University of Toronto

Abstract: Red blood cell (RBC) transfusion carries risks, making it crucial to avoid unnecessary transfusions during cardiac surgery. The impact of biological sex on transfusion and outcomes remains poorly understood, with women being historically underrepresented in cardiovascular trials. Additionally, physicians underestimate cardiovascular risk in women, inducing bias during clinical decision-making. Using data from the Transfusion Requirements in Cardiac Surgery (TRICS) III database, we examined the effect of sex on cardiac surgery outcomes, hypothesizing that sex-based differences occur with respect to transfusion risk, adverse outcomes, and protocol adherence.

The TRICS III trial (NCT02042898) included adult patients undergoing moderate-to-high risk (EuroSCORE I ≥ 6) cardiac surgery. Outcomes included perioperative RBC transfusion incidence, a six-month composite of death, stroke, myocardial infarction, and dialysis-dependent renal failure, and protocol non-adherence rates. Sex cohorts were balanced via propensity score matching and logistic regression models used to determine sex-outcome associations.

RBC transfusion occurred in 73.7% of female versus 58.3% of male patients (adjusted odds ratio [aOR], 1.56; 95% CI, 1.34–1.81), with women more likely to be transfused in the operating room (aOR, 2.14; 95% CI, 1.87–2.50). While composite outcome rates were similar between sexes, women had lower rates of new-onset renal failure (aOR, 0.71; 95% CI, 0.51–0.98). Non-adherent transfusions were more common in women (aOR, 1.38; 95% CI, 1.10–1.74), particularly in the operating room (aOR, 2.74; 95% CI, 1.97–3.80).

Women undergoing moderate-to-high risk cardiac surgery are at higher risk of transfusion relative to male counterparts, specifically in the operating room, despite the presence of a protocolized sex-independent transfusion threshold. Women are also more likely to experience protocol-deviant transfusions, which may be driven by physiological, clinical, or external differences, including clinician bias towards women. Whether greater female transfusion is related to underlying caregiver bias or complex organ specific effects remains to be determined.

ABSTRACTS – ORAL PRESENTATIONS

Oral Presentation Session I – Clinical Research (Dry Bench) Stream

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05 Acute Respiratory Distress Syndrome Following Spinal Cord Injury: Risk Factors and Impact on Clinical Outcomes in a National Multi-Center Cohort

Christopher S Lozano MD, Division of Neurosurgery, Department of Surgery, University of Toronto, Li Ka Shing Knowledge Institute, St Michael's Hospital, Toronto and Institute of Health Policy, Management and Evaluation, University of Toronto; Vishwathsen Karthikeyan MD, Division of Neurosurgery, Department of Surgery, University of Toronto, Li Ka Shing Knowledge Institute, St Michael's Hospital, Toronto and Institute of Health Policy, Management and Evaluation, University of Toronto; Ahmad Essa MD MSc, Faculty of Medicine, Tel Aviv University; Armaan Malhotra MD, Division of Neurosurgery, Department of Surgery, University of Toronto, Li Ka Shing Knowledge Institute, St Michael's Hospital, Toronto and Institute of Health Policy, Management and Evaluation, University of Toronto; Husain Shakil MD MSc, Division of Neurosurgery, Department of Surgery, University of Toronto, Li Ka Shing Knowledge Institute, St Michael's Hospital, Toronto and Institute of Health Policy, Management and Evaluation, University of Toronto; Alexandra De Sequeira BSc, School of Medicine, Royal College of Surgeons in Ireland; Michael Sklaar MD, Interdepartmental Division of Critical Care Medicine, University of Toronto

Introduction: Acute Respiratory Distress Syndrome (ARDS) is a severe pulmonary complication associated with increased morbidity and mortality among spinal cord injury (SCI) patients. This study aimed to evaluate the incidence, identify risk factors, and assess clinical outcomes associated with ARDS in a large contemporary cohort of SCI patients.

Methods: We conducted a multicenter retrospective observational study using data from the American College of Surgeons Trauma Quality Improvement Program (TQIP) from January 2010 to December 2020. The study included patients aged 16 years or older with acute traumatic SCI. ARDS was identified using standardized diagnostic criteria recorded in patient medical records. Multilevel logistic regression analyses, accounting for hospital-level clustering, identified risk factors for ARDS development and associations with secondary clinical outcomes including mortality, sepsis, cardiac arrest, immobility-related complications, and durations of hospitalization, ICU stay, and mechanical ventilation.

Results: Of 55,643 SCI patients, 1,791 (3.2%) developed ARDS. Significant independent risk factors for ARDS included a history of chronic obstructive pulmonary disease (COPD; OR: 1.52), diabetes (OR: 1.35), severe thoracic injury (OR: 1.99), cervical-level SCI (OR: 1.67), motor vehicle trauma (OR: 1.17), and spinal surgery (OR: 1.30). Protective factors were incomplete SCI (OR: 0.34), increased age, female sex, and Glasgow Coma Scale score of 15. ARDS was independently associated with increased odds of mortality (adjusted OR: 3.68), sepsis (OR: 7.57), cardiac arrest (OR: 4.03), and immobility-related complications (OR: 2.90), as well as significantly prolonged hospital stay (11.74 additional days), ICU stay (12.17 additional days), and mechanical ventilation (15.27 additional days).

Conclusions: ARDS is an uncommon but severe complication following SCI, influenced by specific patient comorbidities and injury characteristics. Given its profound impact on mortality, morbidity, and healthcare resource utilization, early recognition and targeted preventive strategies based on identified risk factors are essential to improving clinical outcomes for SCI patients.

ABSTRACTS – ORAL PRESENTATIONS

Oral Presentation Session I – Clinical Research (Dry Bench) Stream

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06 The use of gender frameworks in cardiometabolic disease and nutrition research: a scoping review

Seyedehsara Osia, MPH Candidate (Niutrition and dietetics)*, Dalla Lana School of Public Health, University of Toronto, Toronto, Canada, Toronto 3D Knowledge Synthesis and Clinical Trials Unit, Clinical Nutrition and Risk Factor Modification Centre, St. Michael's Hospital, Toronto, Canada; Zeinab Houshialsadat*, PhD Candidate, Department of Nutritional Sciences, Temerty Faculty of Medicine, University of Toronto, Toronto, Canada, Toronto 3D Knowledge Synthesis and Clinical Trials Unit, Clinical Nutrition and Risk Factor Modification Centre, St. Michael's Hospital, Toronto, Canada; Lamar Elfaki, BSc Candidate, Department of Nutritional Sciences, Temerty Faculty of Medicine, University of Toronto, Toronto, Canada; Aina Oluwatoyin, BSc Candidate, Department of Biochemistry and Immunology, Victoria College, University of Toronto, Toronto, Canada; Dr. Laura Chiavaroli, PhD, Department of Medicine, University of Toronto, Toronto, Canada, Department of Nutritional Sciences, Temerty Faculty of Medicine, University of Toronto, Toronto, Canada, Toronto 3D Knowledge Synthesis and Clinical Trials Unit, Clinical Nutrition and Risk Factor Modification Centre, St. Michael's Hospital, Toronto, Canada
*co-first author

Background: Every Canadian deserves equal access to healthcare, yet the integration of sex and gender-related socio-cultural factors in health research is often overlooked. This hindrance perpetuates health disparities and impedes our ability to address leading causes of morbidity and mortality in Canada, cardiovascular diseases and diabetes, which disproportionately affect women and underrepresented groups. The limited assessment of sex and gender-related factors in health interventions extends to nutrition, the cornerstone of therapy in clinical practice guidelines and the largest modifiable determinant of premature mortality. To address this gap, CIHR recommends Sex and Gender-based Analyses (SGBA+) in health research. They also encourage calculating a gender propensity score to assess gender across the range of gender domains and conducting intersectionality analyses to examine the impact of clusters of variables to identify target populations. To support the uptake of SGBA+ and intersectionality-informed analyses in cardiometabolic diseases (CMD) and nutrition research, we need to understand their current use.

Objective: To assess the current application of gender and intersectionality-informed analyses in CMD and nutrition research.

Methods: We followed the Cochrane Handbook for Systematic Reviews and the PRISMA extension for Scoping Reviews. We searched Medline, EMBASE and the Cochrane Library up to July 2024 to identify studies on cardiometabolic outcomes and applying SGBA+ and gender frameworks. Data was extracted and tabulated by two independent reviewers.

Results: Of 10,985 studies identified, 60 observational studies and no trials were eligible. Three observational studies focused on nutrition using gender-related variables as covariates. Fifty-seven were non-nutrition-related, using gender propensity scores (31), gender-related interaction terms (23), or alternative methods (3).

Conclusion: This review highlights significant gaps in the application of gender and intersectionality-informed analyses in CMD research, especially in trials and in nutrition, calling for greater support to advance uptake and generate the evidence needed to address health inequities.

Funding: CIHR

ABSTRACTS – ORAL PRESENTATIONS

Oral Presentation Session II – Basic Research (Wet Bench) Stream

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07 Integrated Breast Tumor and Placenta -on-a-Chip Model to Define the Molecular Profile of Pregnancy-Associated Breast Cancer

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Abstract: Pregnancy associated breast cancer (PABC) is the most common cancer in pregnancy in which 4% of all breast tumors are coincident with pregnancy with a steady-state increase in occurrence in Canada and globally. The lack of complete molecular profiling of PABC condition raises many challenges for developing nanocarriers that can reach the maternal tumor site while minimizing any potential impact on the fetus, ensuring both safety and efficacy. Therefore, we used FDA-endorsed organ-on-a-chip technology to develop a biomimetic microenvironment of PABC and employed multi-omics and bioinformatic approaches to investigate the molecular profile of the placenta and breast tumor in PABC. Briefly, we developed an integrated dynamic breast cancer-on-a-chip and placenta-on-a-chip model using MCF7 and BeWo cells, respectively. After 24 hours, cells were collected for RNA sequencing and media were analyzed for secreted proteins compared to control dynamic placenta-on-a-chip, breast cancer-on-a-chip models and static controls. Our data showed that the dynamic model more accurately mimics pathological conditions. Dynamic conditions resulted in reduced placental barrier function, as well as decreased placental cell adhesion and tight junction expression under integrated dynamic conditions compared to the static control. In the integrated model compared to the dynamic control models, we observed upregulation of the PI3K-Akt and MAPK signaling pathways in both the placenta and tumor, along with an enhanced placental immune response, indicated by Dectin1 signaling activation, HSPB1 gene upregulation, and extracellular matrix (ECM) degradation. The breast tumor also showed increased ECM formation, characterized by upregulation of collagen complex (COL4A1, COL4A2) and epithelial-mesenchymal-transition EMT-related genes, including APP and LAMC1. In conclusion, the integrated model exhibited greater tumor invasion and metastasis, with the placental barrier showing inflammation and ECM degradation, indicating EMT. Our study introduces an innovative approach for characterizing the molecular profiles of PABC-associated cell lines through the integration of an organ-on-a-chip model and multi-omics analysis, providing a more precise representation of the PABC pathological state.

ABSTRACTS – ORAL PRESENTATIONS

Oral Presentation Session II – Basic Research (Wet Bench) Stream

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08 AI-driven Optimization of Lipid Nanoparticles for Fetal Gene Therapies

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Background: Congenital disorders, such as congenital diaphragmatic hernia (CDH), pose significant challenges in maternal-fetal health. They affect approximately 2% of live births and contribute to 20% of infant mortality. Developing safe and effective gene therapies for congenital diseases requires early intervention with lipid nanoparticles (LNPs) targeted to the diseased fetal organ.

Methodology:
We developed and characterized a diverse library of LNP formulations using microfluidics. Machine learning (ML) models were employed to identify key determinants of LNP size and zeta potential. A total of 41 LNP formulations were screened across different in vitro placental models, generating a dataset of hundreds of transport data points. Our dataset included 18 input features delineating 48 transport experiments. Random Forest algorithms were used to analyze the dataset and identify the top features driving the transport percentage and kinetics. We further evaluated the LNPs' safety and transfection efficiency in placental trophoblasts and fetal lung fibroblasts.

Results:
LNPs showed minimal to no toxicity in fetal and placental cells. The Random Forest algorithm identified the top features driving LNPs placental transport percentage and kinetics; zeta potential and dose were the top features. Leveraging insights from the ML model results, we developed new LNPs formulations that achieved a 622% increase in placental transport. Furthermore, studying LNPs in an integrated placental and fetal lung fibroblasts model showed a strong correlation between zeta potential and fetal lung transfection. The top-performing formulations are currently being assessed as a potential prenatal therapy to rescue abnormal lung development in a CDH rat model.

Conclusions:
Utilizing machine learning has advanced our understanding of LNPs placental transport and delineated key design features for optimization. Our research findings represent a significant step toward establishing the safety and efficacy of LNP-based gene delivery to fetal organs, paving the way for potential prenatal therapies.

ABSTRACTS – ORAL PRESENTATIONS

Oral Presentation Session II – Basic Research (Wet Bench) Stream

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09 YAP/TAZ manipulation influences chemotherapy induced IFN signalling in lung cancer

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Introduction: Chemotherapy is widely used to treat lung cancer (LC) and initially induces tumor regressions in most patients; however, chemoresistance inevitably develops. Thus, an improved understanding of chemoresistance biology is needed to enhance chemotherapeutic efficacy in patients. YAP and TAZ are transcriptional regulators whose overactivation is well-documented to promote LC chemoresistance. Interestingly, some chemotherapies induce antiviral signaling in tumors, which contributes to their anti-cancer effects, and recent studies suggest that YAP/TAZ antagonize antiviral immunity by suppressing induction of type I interferons and interferon stimulated genes (ISG). Therefore, we aim to test the hypothesis that suppression of antiviral signaling by YAP/TAZ represents a previously unrecognized mechanism of chemoresistance.

Methodology: siRNA was used to knockdown YAP and/or TAZ in the lung adenocarcinoma cell lines, H1299 and H2030. Cells were then treated for 48h with chemotherapies including Cisplatin, Doxorubicin, Paclitaxel or Poly(I:C) as a positive control for inducing antiviral signaling. qPCR was used to measure IFN-β as a readout of antiviral signaling and OASL, CXCL10, CCL5 for ISG expression.

Results: Poly(I:C) stimulation of H1299 cells with YAP or TAZ knockdown led to a 2-3-fold increase in IFN-β expression, while combined YAP/TAZ knockdown induced a 5-fold increase in IFN-β relative to cells transfected with non-targeting control siRNA. Similarly, induction of OASL, CXCL10 and CCL5 by chemotherapy was greater in cells with YAP or TAZ knockdown and greatest in cells with combined knockdown. H2030 had similar results with poly(I:C) stimulation leading to a 2-fold increase in IFN-β expression upon YAP knockdown, and 2-3-fold increase uponYAP and/or TAZ knockdown with chemotherapy treatment.

Conclusion: These findings confirm that YAP/TAZ suppress IFN-β induction by Poly(I:C) and ISG induction by chemotherapy, suggesting YAP/TAZ negatively regulate antiviral signaling which could promote chemoresistance.

ABSTRACTS – ORAL PRESENTATIONS

Oral Presentation Session II – Basic Research (Wet Bench) Stream

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10 RhoA is a key mediator of mitochondrial remodeling in Polycystic Kidney Disease via the ROCK/cofilin and formin pathways

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Introduction: Autosomal Dominant Polycystic Kidney Disease (PKD), the most prevalent genetic renal disorder (1:1000), is caused by loss-of-function mutations in polycystin-1 (PC1) or polycystin-2 (PC2) and is characterized by progressive cyst formation and fibrosis. It is hallmarked by robust mitochondrial fragmentation and metabolic changes; however, the mechanisms underlying fragmentation are unknown. Since a) the small GTPase RhoA was implicated in PC loss-induced cystogenesis and b) RhoA activation is central for the fibrogenic epithelial reprogramming, we hypothesized that 1) RhoA and its downstream effectors might be key regulators of mitochondrial dynamics in PKD, and 2) mitochondrial fragmentation per se might contribute to fibrogenesis.

Methodology: We used PC1/2 downregulation by siRNA in LLC-PK1 tubular cells or cell lines derived from a PKD patient and healthy control. Mitochondrial fragmentation was analyzed by automated confocal morphometry (IMARIS) on GFP/RFP-labeled mitochondria, and by electron microscopy. RhoA, its downstream effectors, and the fission machinery were all manipulated genetically or pharmacologically.

Results: PC1 or PC2 loss induced robust mitochondrial fragmentation, which was prevented by RhoA downregulation or inhibition. Conversely, constitutive RhoA was sufficient to induce fission. PC1/PC2 loss-triggered mitochondrial fragmentation was dependent on 1) dynamin-related protein-1 (DRP1), 2) RhoA-associated kinase (ROCK) and its downstream target, the severing protein cofilin; and 3) the activity of formins, key actin-regulating RhoA effectors. Mitochondrially targeted, constitutively active formins induced fragmentation, while ablating their F-actin polymerization capacity exerted a dominant negative effect. Furthermore, we found increased levels of mitochondrial fragmentation in PKD patient cells compared to healthy controls. Importantly, pharmacological formin inhibition restored mitochondrial network integrity in PKD. Finally, inhibition of fragmentation by DN-DRP1 significantly reduced the induction of several profibrogenic genes.

Conclusions: We define a new pathway responsible for PC loss-induced mitochondrial fragmentation. This RhoA-dependent, DRP1-mediated, formin-promoted process may be critical for the ensuing metabolic alterations and fibrogenesis.

ABSTRACTS – ORAL PRESENTATIONS

Oral Presentation Session II – Basic Research (Wet Bench) Stream

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11 Lipoprotein(a) and the Arterial Endothelium: Elucidating Mechanisms of Residual Cardiovascular Risk

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INTRODUCTION: Atherosclerosis is one of the leading causes of death in Canada and is initiated by the deposition of lipids, particularly low-density lipoprotein (LDL), underneath the arterial endothelium. This occurs by a receptor-and caveolae- mediated vesicular traffic known as transcytosis requiring scavenger receptor class B type I (SR-BI) and activin receptor-like kinase (ALK1). Mortality from atherosclerosis remains high despite optimal lowering of circulating LDL levels, indicating residual cardiovascular risk. Lipoprotein(a) [Lp(a)] is a lipoprotein structurally similar to LDL that is significantly more atherogenic; its levels are typically unaffected by cholesterol-lowering therapies. Although Lp(a) has been recognized as a cardiovascular risk factor for years, the mechanisms by which it promotes atherosclerosis are not yet understood.

HYPOTHESIS: Lp(a) may undergo transcytosis by human coronary artery endothelial cells (HCAECs) and accumulate in the arterial wall, contributing to atherosclerosis development.

METHODS AND RESULTS: Using Total Internal Reflection Fluorescence (TIRF) microscopy and HCAECs, Lp(a) was discovered to undergo transcytosis. Competition with unlabeled lipoprotein demonstrated that Lp(a) transcytosis is receptor-mediated and competes with LDL for the same transcytosis receptors. Knockdown of SR-BI or ALK1 using siRNA, induced and reduced Lp(a) transcytosis, respectively. Transient overexpression of ALK1 appears to increase Lp(a) transcytosis. Knockdown of caveolar constituent caveolin-1 (Cav-1) using siRNA reduced Lp(a) transcytosis substantially. In vivo, acute and dose-dependent deposition of Lp(a), but not dextran (control for paracellular leakage), was measured in the atheroprone region of the murine aortas via confocal microscopy.

CONCLUSIONS: Lp(a) can undergo receptor-mediated endothelial transcytosis, potentially via ALK1 and Cav-1. Validation of ALK1-mediated Lp(a) transcytosis will be performed in vivo using tissue-specific knockout animals. Mutations in the ALK1 extracellular domain will be performed to investigate direct binding between ALK1 and Lp(a), in vitro. Understanding Lp(a) transcytosis across the arterial endothelium can help elucidate how Lp(a) may contribute to residual cardiovascular risk.

ABSTRACTS – ORAL PRESENTATIONS

Oral Presentation Session II – Basic Research (Wet Bench) Stream

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12 Loss of microglial homeostatic TGFβ production induces myelin dynamics that mimic multiple sclerosis

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Abstract: Multiple sclerosis (MS) is a neurodegenerative disease caused by damage to myelin and myelin-forming oligodendrocytes in the central nervous system (CNS), and is characterized by progressive motor, sensory, and cognitive deficits. While this damage is thought to be mediated by peripheral immune cells, targeting these immune cells does not slow progression, suggesting other mechanisms at play. Microglia are thought to play a role in MS pathogenesis, as they downregulate homeostatic genes early in disease, suggesting a loss of function. They are also dysregulated at sites of myelin damage that have no immune infiltration, suggesting a microglial role in myelin damage initiation. We investigate how loss of microglial function influences myelin and oligodendrocyte health using Csf1r-FIREΔ/Δ mice, which constitutively lack microglia. We find that absence of microglia is sufficient to mimic myelin dynamics observed in MS. We observed focal white matter demyelination in Csf1r-FIREΔ/Δ mice at 6 months, followed by remyelination, and a recurrent demyelination at 12 months that persisted. Demyelination was preceded by the emergence of a Serpina3n+ oligodendrocyte population, and was concurrent with decline of this population and upregulation of ferroptosis markers. Ablation of TGFβ from microglia was sufficient to induce Serpina3n+ oligodendrocyte loss and myelin damage. We propose that the absence of microglial homeostatic function causes the appearance of a pathological oligodendrocyte population whose death may drive myelin damage in MS.

ABSTRACTS – POSTER PRESENTATIONS

Poster Session

01 Brain myeloid cells regulate oligodendrogenesis and myelination in the developing central nervous system

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Abstract: Myelin is the insulating membrane surrounding axons which is formed by mature oligodendrocytes starting in the second trimester in humans and in the early postnatal period in mice, and is crucial for central nervous system (CNS) function. However, there is still lack of understanding of the fundamental mechanisms contributing to developmental myelination. CNS-resident myeloid cells are a heterogeneous group, encompassing microglia, border-associated macrophages (BAMs) in the meninges, the choroid plexus and the perivascular space. Together, these cells are promising candidates as their depletion impairs oligodendrogenesis and myelination; nonetheless, the specific myeloid cell subtype driving these processes is unclear. Our recent work using a mouse model specifically lacking microglia indicated that these alone are not required for developmental oligodendrogenesis and myelination. Here, we uncover the contribution of BAMs to myelin development. We identified that BAM numbers increase coinciding with oligodendrogenesis and myelination in mouse and human developing brains. By developing two new transgenic models of specific depletion of BAMs, we observed reduced oligodendrogenesis at early postnatal ages. Overall, our study reveals a novel cellular interaction facilitating oligodendrogenesis and myelination, highlighting that different phases of myelination are regulated by distinct CNS myeloid cell subsets.

02 Identifying ultrasound and photoacoustic imaging biomarkers from Mitochondrial Therapies applied to Kidney Transplants

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Abstract: Ischemia reperfusion injury (IRI) occurs during kidney transplantation because of the disruption and re-introduction of blood flow to the organ. We propose a remedy for minimizing IRI using mitochondrial transplant (MTx) that re-establish/regulate the biological processes in the electron transport chain and calcium transport to prevent production of reactive oxygen species, reduce cellular apoptosis, and improve organ functionality/repair. To quantify the effects of MTx treatments on IRI, ultrasound-guided photoacoustic imaging (USPA) can be used to produce high-resolution, structural and functional kidney images.
USPA imaging will be performed on 10 pig kidney transplantations (5 per experimental group) using a VisualSonics VevoLAZR 2100. In each experiment, two pigs are used: the first pig donates blood and the other pig donates and receives the kidney (auto-transplantation). In situ kidney scans at baseline, 30 minutes post-renal artery/vein clamp, and 0-day/3-day post transplant are collected at wavelengths 750/806/850nm. Ex vivo scans, while the kidney is placed on a closed circulating pump with blood fused with mitochondria or saline solution, are collected at the 3 wavelengths for the lower-, inter-, and upper kidney poles for time points 30 minutes, 1, 2, 3, 4, and 5 hours.
USPA amplitudes and maps of kidney sO2 will be generated to evaluate the efficacy of MTx treatments over time. Comparisons of USPA data to the clinical "gold-standard" histological metrics will further quantify the efficacy of MTx treatments. By analyzing these trends/changes, we believe this project has the potential to predict and improve kidney transplantation outcomes.

03 The role of erythropoietin signaling in the liver

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INTRODUCTION: Erythropoietin (EPO) regulates red blood cell production and may have beneficial roles in obesity and type 2 diabetes. People with diabetes often have anemia and EPO deficiency due to renal impairment. Correction of anemia with EPO improves exercise tolerance, pancreatic B-cell function, and quality of life. Disruption of EPO signaling in extra-hematopoietic cells leads to obesity, while EPO treatment can protect against diabetes. The role of hepatic EPO signaling in type 2 diabetes remains unclear.

OBJECTIVES: We aim to identify the role of hepatic EPO in a high-fat diet (HFD)-induced diabetes model. We hypothesize that hepatic EPO signaling protects against fatty liver disease and diabetes via cytoprotective effects.

METHODS: We generated hepatocyte-specific erythropoietin receptor knockout mice (albcreEPOR-/-) using the Cre-loxP system, with littermate controls (albcreEPOR+/+). Mice were fed chow or HFD for six months and assessed for glucose homeostasis via glucose and insulin tolerance tests. Body composition was analyzed by weighing adipose tissue and liver.

RESULTS: Under chow diet, albcreEPOR-/- mice showed no differences in body weight or glucose metabolism compared to controls. Under HFD, albcreEPOR-/- mice had impaired glucose tolerance. Male knockout mice exhibited less fatty liver than

controls, while females were more susceptible. Estrogen receptor ESR-1 played a vital role, and lipogenic genes were upregulated in female knockout mice. Future work will examine liver fibrosis and markers of cell death and inflammation.

CONCLUSIONS: EPO plays a crucial role in glucose homeostasis and fat accumulation under HFD conditions. The sex-specific effects highlight the involvement of ESR-1 and increased lipogenic gene expression in females.

04 Deciphering CD47-driven platelet-tumor crosstalk and its associated transcriptomic changes in NSCLC metastasis

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Abstract: CD47 is overexpressed and associated with poor prognosis in non-small cell lung cancer (NSCLC). Most studies of CD47 have focused on its role in promoting tumor immune evasion although it has been shown to influence cancer metastasis. Since platelets are known to promote tumor cell dissemination and platelets can bind to other cells via homotypic CD47 interactions, we aimed to investigate the hypothesis that CD47 promotes NSCLC metastasis through interactions with platelets. CRISPR/Cas9 was used to knockout (KO) CD47 in a murine (LLC) and human (H1299) NSCLC model. Scratch assays and tail-vein injections in syngeneic mice were done to assess the effects of CD47 KO on migration and metastasis. Cancer cell binding and activation of platelets was measured by flow cytometry. An in vivo platelet depletion study was performed on the LLC tail vein model using an anti-GPIIbIIIa antibody delivered every 3 days. Tumor metastasis was monitored using bioluminescence imaging. Bulk RNA-sequencing was performed on cell sorted tumor cells to investigate transcriptomic changes related to metastasis. CD47 KO impaired migration of LLC and H1299 cells in vitro, and significantly prolonged metastasis-free survival of mice in vivo. Binding assays revealed decreased platelet binding to LLC cells with CD47 KO, and decreased platelet activation in KO cells relative to wildtype controls. In vivo, LLC CD47 KO together with platelet depletion abolished tumor growth. RNA-sequencing of dissociated lung tumors show negative enrichment of epithelial-mesenchymal transition (EMT) and coagulation pathways, consistent with the metastasis and platelet phenotypes seen. Our findings indicate that CD47 promotes migration and metastasis in NSCLC, and that CD47 may influence lung cancer cell interactions with platelets. CD47-targeted therapy may inhibit lung tumors by antagonizing metastatic spread in addition to immune evasion. Future experiments will include studies to characterize the platelet activating factors being secreted by WT and CD47 KO cells.

05 Monocytes reduce remyelination efficiency

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MS is a neurodegenerative disease resulting from damage to the central nervous system (CNS), termed demyelination. The efficiency of the reinstatement of myelin, known as remyelination, decreases with MS progression, leading to axon dysfunction and loss. This is due in part to impaired function of oligodendrocytes, however the underpinning mechanisms are unclear. CNS myeloid cells, such as blood monocytes, are promising candidates for the regulation of remyelination as they are required for oligodendrocyte responses during remyelination, yet are dysregulated in MS. Here, we asked how monocytes influence remyelination. We assessed the infiltration of monocytes into lysolecithin-induced focal demyelinated lesions of the adult mouse corpus callosum by flow cytometry and use of transgenic mice that have fluorescently labelled

'inflammatory' classical monocytes (Ccr2RFP/+). To determine the role of monocytes in remyelination, we lesioned mice where monocyte egress from bone marrow is impaired (Ccr2-/-) and assessed cellular and myelin responses by immunofluorescence and electron microscopy. We identified the molecular mechanisms by which monocytes regulate remyelination by RNA sequencing of mouse lesion cells, data-mining of MS lesion monocyte transcriptomes, and blood MS monocyte profiling. The role of monocytic Wnt signaling in remyelination was assessed through transgenic and pharmacological interventions in lesioned mice. We found that monocytes are present throughout remyelination. We discovered that classical monocytes are required for oligodendrocyte differentiation and myelin protein expression, yet impaired myelin production. We identified a Wnt signature in lesion monocytes, which was also observed in MS blood and lesion monocytes. Remyelination was enhanced after blocking the ability of monocytes to release Wnt. We uncovered that monocytes regulate remyelination efficiency, with non-redundant roles from microglia. Monocytes decrease myelin production via Wnt signaling, thereby decreasing overall remyelination efficiency. Our findings reveal monocytes and the Wnt pathway as novel therapeutic targets to enhance remyelination in MS.

06 Changes in Stress and other Mental Health Outcomes among Syrian Refugee Women from Before to During the COVID-19 Pandemic

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Introduction: Syrian refugee women in Canada may face mental health challenges, particularly during crises like the COVID-19 pandemic. However, limited research has explored how the pandemic affected newcomers' mental health. We will examine changes in stress, depression, and emotional well-being among Syrian refugee women pre-pandemic and during the pandemic, highlighting key social determinants influencing mental health outcomes.

Methodology: The data used is part of the nationwide longitudinal SyRIA.lth study and will be used to analyze self-reported mental health data from Syrian refugee women settled in Canada with sample sizes of over 1600 in included waves of data. The primary outcome is perceived stress (PSS-10), with secondary outcomes including depression severity (PHQ-9) and emotional well-being (RAND-36 subscale) in women. The key predictor is the pandemic period (pre-pandemic vs. during the pandemic). Covariates include age, marital status, employment status, education level and financial insecurity (frequency of difficulty paying for basic needs). We will estimate the association between the pandemic period and mental health outcomes using multivariable linear regression models, adjusting for covariates. We will explore how the relationships between the pandemic and stress vary across social support, city of residence and financial security strata.

Results: We will use regression analyses to quantify the impact of the pandemic period on mental health outcomes, estimating adjusted associations with key social determinants. We anticipate our findings to identify factors that are associated with exacerbated or mitigated stress, depression, and emotional well-being among refugee women.

Conclusions: We will contribute to understanding the pandemic's mental health impact on newcomers in Canada, contributing to broader literature informing policies and interventions. By identifying social determinants that influence

mental health, we aim to contribute to the knowledge of social determinants associated with worse mental health outcomes in newcomer populations and how crisis situations may affect these outcomes.

07 KIFC1 inhibition is a promising therapeutic strategy in lung cancers with centrosome amplification

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Lung cancer (LC) is the leading cause of cancer-related deaths in Canada, emphasizing the need for novel treatments targeting hallmark features of LC. Genomic instability is a hallmark of LC that promotes tumor progression, and can arise from centrosome amplification (CA). While two centrosomes allow for equal division of chromosomes during mitosis in non-malignant cells, LC cells often have abnormal increases in centrosome number. While CA can confer advantages to LC cells by promoting genomic instability, it can also cause lethal multipolar cell divisions. This necessitates a reliance on CA-coping mechanisms which represent potential therapeutic targets. Using a CRISPR loss-of-function (LOF) screen in LC cells with drug-induced CA, we identified KIFC1 as a CA-specific vulnerability in LC. A series of validation experiments confirmed that LC cells with CA are dependent on KIFC1 for their survival due to its role in clustering extra centrosomes during mitosis.

Currently available inhibitors have demonstrated an ability to inhibit KIFC1 but they have been reported to have poor specificity for KIFC1. We sought to develop novel inhibitors with improved pharmacological properties. In a collaborative effort, we are testing two new KIFC1 inhibitors (HCE56 and HCE57, synthesized by Dr. Hou), for their abilities to suppress KIFC1 function and reduce viability in LC cells with CA. To date, we have confirmed that: HCE56 inhibits KIFC1's centrosome clustering function; HCE56 induces greater lethality than the commercially available KIFC1 inhibitor, AZ82; and HCE56 is not lethal in non-malignant cells. These findings support the development of KIFC1-targeted therapy for LC with CA. Ongoing work continues to characterize the anti-cancer properties and specificity of these novel KIFC1 inhibitors.

08 The Impact Of Prostaglandin E2 on Fibro-Adipogenic Progenitors Activation

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

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

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

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

09 Crosstalk Between Endothelial and Perivascular Stromal Cells: Orchestrating Myofibroblast Activation

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Introduction: Vascular endothelial cells (ECs) are first responders launching organ repair following injury, infection, and inflammation. When these conditions endure, life-threatening fibrosis develops. Perivascular mesenchymal stromal cells (MSCs) in proximity to ECs provide structural support in normal vessels and are activated into myofibroblasts upon injury. Central for myofibroblast activation is the locally confined extracellular activation of profibrotic TGF-β1. Whether ECs directly activate MFs and if TGF-β1 is involved in the process is unknown. The objective of the study is to investigate the crosstalk between ECs and MSCs in the perivascular fibrotic niche.

Methodology: To evaluate the potential of ECs in producing and presenting latent TGF-β1, we performed a meta-analysis on six datasets comprising 123 single-cell RNA-sequencing (scRNA-seq) samples from normal (n=58) and fibrotic (n=65) lung tissues. To investigate if ECs activate MSCs and if myofibroblast activation is locally confined, we immunostained co-cultures of primary ECs and MSCs for the EC marker CD31 and the myofibroblast marker α-SMA. Expression of molecular components of TGF-β1 presentation and activation were assessed after sorting of EC and MSC for CD31 and CD90, respectively.

Results: In silico analysis revealed that blood vascular ECs most highly express LRRC32 of all TGF-β1 presenting proteins and compared to other cell types in lung tissues. In co-culture monolayers, CD31-positive ECs segregate from MSCs to form linear 'capillary-like' structures surrounded by MSCs. MSCs in proximity to ECs express higher levels of α-SMA than those farther away or in monocultures. Results indicated an increase in the expression of LRRC32 (GARP) in ECs but not MSCs after co-culturing, while □-SMA expression increases in MSCs. These results suggest that contact with ECs activates MSCs into myofibroblasts.

Conclusions: Deciphering perivascular MSC-EC interactions and their perturbation can help to design targeted therapies for vascular disorders and fibrosis.

10 Identifying potential mechanisms whereby knocking down YAP in adipocytes improves glucose metabolism

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Background: Yes-associated protein 1 (YAP) is a transcriptional co-activator of the Hippo signaling pathway, which regulates cell functions. Previously, we showed that YAP protein was increased in adipose tissue from humans with and mouse models of type 2 diabetes. To study the role of YAP in adipocytes and glucose homeostasis, we used an adiponectin-Cre loxP recombination system to generate adipocyte-specific YAP knockout mice (AdipoqYAP-/-). When fed a high-fat diet (HFD), knockout mice had improved glucose tolerance compared to littermate controls (AdipoqYAP+/+), showing that lowering Yap1 in adipocytes prevents glucose intolerance with metabolic stress. Nonetheless, how adipocyte YAP regulates glucose metabolism remains unclear.

Purpose and Hypothesis: The objective of this study is to identify potential novel mechanisms to how knocking down Yap1 in adipocytes improves glucose tolerance. We hypothesize that lowering YAP gene expression improves glucose metabolism by increasing beta-arrestin 2.

Methods: To gain insight into the role of Yap1 knockdown on the cell transcriptome and functional relevance, RNA sequencing was conducted. RNA was isolated from perigonadal adipose tissue obtained from mice with adipocyte-specific Yap1 knockdown and littermate controls. Sequencing was performed on an Illumina NovaSeq 6000 instrument (150 cycles). Transcript abundances were estimated and the FPKM value was calculated using StringTie and the R package Ballgown, respectively.

Results: Differentially expressed genes and transcripts were filtered by fold-change (cutoff 1.5), p-value (≤ 0.5) and FPKM (≥ 0.5 mean in one group). As expected, Yap1 was significantly downregulated in adipose tissue. Notably, β-arrestin 2, a multifunctional adapter protein was also differentially expressed (1.669-fold) with YAP knockout. Moreover, Western blotting and qPCR conducted on proteins and RNA extracted from subcutaneous and visceral fat confirmed that β-arrestin 2 proteins increased in knockout mice versus control mice. This was associated with improved adipose tissue-specific insulin sensitivity demonstrated by increased levels of phosphorylated Akt.

11 Dysfunctional oligodendrocytes accumulate in human cognitive decline

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Abstract: Cognitive decline is a hallmark of aging and severely impacts quality of life, for which we lack therapeutic interventions. However, why some individuals experience more severe cognitive decline with aging than others is unclear. Although brain white matter pathology has been associated with decreased cognition, the underlying changes in myelin and oligodendrocytes remain unknown.

Here, we investigated the neuropathological and transcriptomic changes in human white matter associated with individual rates of cognitive decline in aging. We find that worse cognitive trajectories in aging associate with hypermyelination, axonal pathology, and greater numbers of oligodendrocytes with impairments in NRF2 signaling. Disruption of NRF2 in oligodendrocytes was sufficient to mirror myelin and axonal pathology in aged mice.
These findings uncover a role for oligodendrocyte dysfunction in contributing to the neuropathology associated with cognitive decline, and highlight targeting of the NRF2 pathway in oligodendrocytes as a potential avenue to preserve cognition in aging.

12 Triglyceride- and Cholesteryl Ester-Rich Lipid Droplets Exhibit Different Effects on Low Density Lipoprotein Transcytosis in Endothelial Cells

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Abstract: The initial stage of atherosclerosis involves low-density lipoprotein (LDL) crossing individual arterial endothelial cells in an active process termed transcytosis. While it is well established that LDL transcytosis is essential for the pathogenesis of atherosclerosis, the physiological function of LDL transcytosis remains unclear. We speculate that LDL transcytosis is involved in intracellular lipid trafficking and storage in compartments known as lipid droplets (LDs), which are organelles essential for sequestering excess lipids to prevent lipotoxicity. It is possible that LDL may deposit or sequester lipids in or out of LDs during transcytosis to help maintain cellular lipid homeostasis, as abnormal accumulation of LDs can disrupt cellular function and cause inflammation. To determine if there is a relationship between LDL transcytosis and LDs, triglyceride (TAG)- or cholesteryl ester (CE)-rich LDs were induced in human coronary artery endothelial cells (HCAECs) with oleic acid or cholesterol and subsequently subjected to total internal reflection fluorescence microscopy (TIRFM) to measure LDL transcytosis. Cells with TAG-rich LDs performed significantly less LDL transcytosis compared to the control, while cells with CE-rich LDs exhibited a significant increase in LDL transcytosis. The differential effects of TAG- and CE-rich LDs were found to be specific to LDL transcytosis, as albumin transcytosis was unaffected in HCAECs with TAG- and CE-rich LDs. Through LDL uptake assays and TIRFM, it was revealed that LDL uptake was not affected in HCAECs with TAG-rich LDs, but the amount of LDL at the basolateral membrane, as well as LDL exocytosis, was significantly lower compared to the control. Conversely, HCAECs with CE-rich LDs exhibited a significant decrease in LDL uptake, yet there were significantly more LDL particles at the base of the cell, as well as increased exocytosis of LDL. The detailed mechanisms of how TAG- and CE-rich LDs affect LDL transcytosis are currently under investigation.

13 Vitamin D Mediated Mechanisms in Autoimmune Disease

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Background: Autoimmune disorders (AIDs) are caused by numerous genetic and environmental factors. Identified genetic risk loci are enriched in immune cells. Low Vitamin D (VD) is strongly associated with multiple sclerosis (MS): high latitude and low ultraviolet exposure predict higher MS risk. Mendelian randomization studies confirm low serum VD as a causal risk factor for MS. We do not know how low VD causes MS, but VD is a potent transcriptional regulator in immune cells.

Purpose and Hypothesis: We hypothesize that pathways regulated by VD in immune cells are relevant to autoimmune pathogenesis. To identify AID mechanisms, we propose to characterize the transcriptional effects of VD in human peripheral blood mononuclear cells (PBMCs) at single-cell resolution.

Methods: We collected blood from 10 healthy subjects. We isolated and cultured PBMCs with and without active VD (1,25(OH)2-D3). We assessed gene expression at 8-, 24-, 48- and 72-hours using the 10x Flex assay. After aligning to the human genome, quality control, and identifying cell types, we obtained data on 563,520 PBMCs.

Results: We identified 440 differentially expressed genes (DEGs), 365 in Monocytes (FDR < 0.05, logFC > 1) and 75 (FDR < 0.05) in NK- (23), CD4 T- (28), CD8 T- (23) and B-Cells (4). Several of the DEGs have been previously nominated by MS GWAS studies, notably CYP24A1, a VD response gene, in Monocytes at 8 (FDR = 4.1×10-5, logFC = 6.79) and 24 hours (FDR = 1.0×10-13, logFC = 7.79), suggesting that identified DEGs may be affected through VD-regulated pathways. Preliminary pathway analysis presents varied activity across different immune cell types consisting of activation of metabolic pathways and a complex regulatory pattern of inflammatory and differentiation pathways. We aim to identify how these transcriptional changes may impact AID relevant immune activity.

14 Differential regional vulnerabilities to age-related myelin pathology in human brain

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Abstract: Healthy myelin is essential for healthy cognition, with different white matter brain regions controlling distinct cognitive domains. It is unknown whether cognitive decline with age reflects region-specific impacts on myelin integrity. Here, we compared myelin integrity with aging in different white matter regions of the human brain involved in cognitive function, using electron microscopy and ultrastructural analysis. We found no loss of myelin integrity in the aged vs young frontal white matter with respect to accumulation of myelin abnormalities, density and size of myelinated axons, and myelin thickness. Notably, we found a relative protection of myelin integrity in frontal vs occipital and central white matter regions in aged brains. Interestingly, degree of cognitive decline in the 15 years prior to death was not correlated with myelin properties in frontal white matter, in contrast to a positive correlation with central white matter. We hypothesize that this protection may be due to regional differences in axon size, with frontal white matter having smaller axons. Accordingly, mouse central white matter showed a decrease in large diameter axons at an age when cognitive decline is documented. These results suggest reveal regional differences in myelin pathology with age, and suggest large diameter axons as being more vulnerable to age-associated loss of myelin integrity associated with cognitive impairment.

15 Investigating YAP/TAZ-mediated regulation of the spindle assembly checkpoint in lung cancer

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Abstract: YAP/TAZ are paralogous transcriptional co-regulators frequently overactivated in lung cancer (LC). In the nucleus, YAP/TAZ bind TEAD transcription factors to activate transcriptional programs associated with proliferation, metastasis, immune evasion, epithelial-to-mesenchymal transition, and chemoresistance. Studies also suggest that YAP/TAZ regulate the spindle assembly checkpoint (SAC), which maintains genome integrity during mitosis by delaying anaphase until all

chromosomes are properly attached to the mitotic spindle. However, the mechanism by which YAP/TAZ regulate the SAC and the relevance of this function in LC remain unclear. Our recent studies suggest that TAZ can bind to BUB3, a key SAC mediator, and its homolog RAE1. Therefore, we hypothesize that YAP/TAZ regulate the SAC through a transcription-independent mechanism involving direct interactions with SAC proteins.

To assess the effect of YAP/TAZ on SAC activation, we depleted or overexpressed YAP/TAZ in LC cells, and quantified mitosis duration using live-cell microscopy. TAZ knockdown induced a 14% increase while combined YAP/TAZ knockdown induced a 35% increase in mitosis duration ($p<0.001$). Surprisingly, TAZ overexpression also caused a 13% increase in mitosis duration ($p<0.0001$). To further investigate TAZ-mediated SAC regulation, we established a system for inducible expression of several TAZ variants including transcription-dead, nuclear import-deficient, and truncated TAZ constructs. We have confirmed that inducing wild-type TAZ increases transcription of TAZ targets and that target gene expression is diminished when the TAZ variants are induced. This demonstrates the utility of our system for uncoupling transcription-dependent and –independent effects of TAZ on SAC function, which we are currently investigating.

An increase in mitosis duration for both knockdown and overexpression suggests that optimal amounts of YAP/TAZ are required for proper SAC function. Using our TAZ variant system, we expect to elucidate transcription-independent effects and specific functional domains required for TAZ-mediated SAC regulation, which could reveal new ways in which YAP/TAZ contribute to tumour-promoting mitotic abnormalities.

16 Midbrain somatostatin cells stimulate breathing and motor activity in rodents in vivo

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Abstract: Breathing is an essential function that is automatically generated by neural circuits in the medulla. Although breathing is mostly an automatic process, it is highly flexible and can be synchronized with behaviors requiring activation of respiratory muscles such as sniffing or vocalization. Respiratory neural circuits receive projections from many brain regions so respiratory muscles can be modulated to accommodate motor behaviors. The periaqueductal grey matter (PAG) located in the midbrain sends projections to the medulla. While the PAG is not involved in the automatic production of breathing, it is involved in coordinating autonomic functions such as breathing with behaviours. However, the types of PAG neurons involved in breathing and their functions remain unclear. Somatostatin (SST), an inhibitory neuropeptide found in the medulla but also in the ventrolateral PAG (vlPAG) may be involved in modulating breathing. In addition, SST PAG cells are involved in neuropathic pain. Here, we aim to determine the role of SST vlPAG neurons in modulating respiratory rhythm and their role in motor behaviours such as motor response to pain.

To this aim, we used optogenetics to selectively activate SST vlPAG cells while measuring respiratory activity with whole-body plethysmography and motor behaviors with video recording in freely-behaving mice. We observed that photostimulation of SST vlPAG cells stimulates breathing while simultaneously increasing locomotor activity. To determine whether changes in respiratory activity were due to increased motor activity, we performed the same experiments in anesthetized mice and found that photostimulation of SST vlPAG neurons increased respiratory activity. Our results suggest that stimulation of SST vlPAG neurons independently modulated respiratory and motor activity and may be involved in the modulation of respiratory muscle activity to produce non-respiratory behaviors.

17 Modeling drug tolerance and minimal residual disease to discover effective therapeutic combination strategies for EGFR-mutated lung cancer

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Abstract: Resistance to EGFR-targeted therapy is a barrier to improving survival rates for non-small cell lung cancer (NSCLC) patients whose tumors have activating EGFR mutations. Resistance to EGFR tyrosine kinase inhibitors (TKIs) emerges from drug-tolerant persister cells (DTPs) that survive TKI therapy and manifest as minimal residual disease in patients, ultimately leading to fatal tumor recurrence. DTPs are a rare population of cancer cells in a reversible, slowly proliferating state that survive targeted therapy. Upon TKI withdrawal, they exit the DTP state to recommence rapid proliferation and aggressive tumor growth. Thus, DTPs provide a reservoir of surviving cells from which outright resistance driven by acquired genetic alterations arises. However, such mechanisms are poorly understood in lung adenocarcinoma (LUAD). To bridge this knowledge gap, we developed robust in vitro and in vivo LUAD models of drug tolerance induced by the standard-of-care EGFR TKI, Osimertinib (Osi), for comprehensive genetic and functional characterization.
To date, Osi response in 3 EGFR-mutant models has been characterized [PC9, HCC4006, and one patient xenograft-derived cell line, X137CL]. Osi induced apoptosis and G0-G1 arrest in these models in vitro, consistent with the slow cycling nature of DTPs. In vivo, Osi treatment induced strong tumor regressions, followed by relapse upon drug withdrawal, indicating these models are appropriate for studying DTP biology. These DTP models will be profiled with single cell RNA sequencing to understand the DTP transcriptional landscape, as well as CRISPR loss-of-function screens to identify their genetic vulnerabilities. Genetic and functional characterization of these DTP models has the potential to identify mechanisms enabling drug tolerance that could be targeted to prevent TKI resistance from developing. Therefore, this study has great potential to reveal novel interventions for preventing tumor relapse following TKI therapy, which could help to improve survival rates of patients with EGFR-mutant lung cancer.

18 Investigating the efficacy of a single-session psychotherapy for suicide risk in adults

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INTRODUCTION: Suicide is a serious public health concern in Canada, with suicide rates remaining stagnant over the past decade. Limited access to effective interventions is a major barrier to suicide prevention. Single-session suicide psychotherapy offers a cost-effective approach with high treatment engagement. “Brief Skills for Safer Living” (Brief-SfSL) is a novel 90-minute, single-session intervention designed to reduce suicide risk by addressing an individual’s “suicide narrative,” developing personalized skills, and creating a safety plan. It can be delivered in-person or virtually, making it adaptable to various healthcare settings and reducing resource demands. The main objectives of this study are to (1) determine the efficacy of Brief-SfSL at reducing suicidal ideation in adults over a three-month follow-up period, (2) assess the impact of Brief-SfSL on cognitive control and social cognition, and (3) examine its effects on additional suicide risk factors.

METHODOLOGY: The study will be conducted as a three-month, randomized controlled trial (RCT) recruiting adults across Canada reporting suicidal ideation. Participants will be randomized to one of two groups: B-TAU (Brief-SfSL + treatment as usual; n=75) and WL-TAU (treatment as usual; n=75). The study will be conducted virtually using Zoom for Healthcare and REDCap. Participants will complete questionnaires assessing suicidal ideation, depression, anxiety, anhedonia, functioning, and social connectedness, as well as gamified behavioral tasks evaluating cognitive control and social cognition.

EXPECTED RESULTS: Brief-SfSL is expected to significantly reduce suicidal ideation and improve cognitive control and social cognition at the three-month follow-up. The treatment group is also expected to exhibit improvements in suicide risk factors compared to the control group.

CONCLUSION: These findings will offer valuable insights into Brief-SfSL's effectiveness, supporting its integration into various healthcare settings. This study aims to expand access to effective suicide interventions and improve outcomes for individuals at risk of suicide.

19 The effects of HMGB1 nuclear depletion on the DNA damage response following traumatic brain injury

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Abstract: High mobility group box protein 1 (HMGB1) plays dual roles in cellular physiology: under normal conditions, it stabilizes chromatin, regulates transcription, and supports DNA repair, while during cellular stress or injury, it translocates from the nucleus and functions as a proinflammatory cytokine. This study investigated the temporal progression of nuclear HMGB1 loss following traumatic brain injury (TBI) in 250g male rats and examined correlations with DNA damage response proteins.
Following TBI, HMGB1 translocation from nucleus to cytoplasm occurred rapidly in neurons, with significant nuclear depletion observed within 6 hours post-injury. Quantitative immunohistochemistry and Western blot analysis confirmed significant decreases in nuclear HMGB1 expression at both 6 and 24 hours compared to controls. By 7 days post-injury, approximately 20% of neurons exhibited complete absence of nuclear HMGB1 expression.
Neurons lacking nuclear HMGB1 demonstrated positive labeling for multiple stress indicators, including hypoxia-inducible factor 1-alpha (HIF1α), poly(ADP-ribose) polymerase (PARP), and phosphorylated histone H2AX (γH2AX). Additionally, a primary neuronal cell culture model using oxygen-glucose deprivation injury was established to reproduce these findings. This in vitro model successfully demonstrated HMGB1 translocation from nucleus to cytoplasm, along with corresponding increases in PARP expression, γH2AX, and HIF1α, as confirmed by Western blot analysis and confocal microscopy.

The cell culture model will be further utilized in conjunction with HMGB1 knockdown siRNA to directly assess the impact of nuclear HMGB1 loss on DNA damage repair mechanisms following injury. The temporal relationship between HMGB1 nuclear translocation and expression of DNA damage markers indicates a mechanistic link between injury-induced HMGB1 loss and subsequent DNA damage. These findings highlight a potentially important injury response pathway with significant implications for the long-term genetic integrity of surviving neurons following TBI.

20 The proto-cadherins Dchs1 and FAT4 mediate profibrotic polarization of macrophages in direct contact with fibrogenic fibroblasts

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Background: Both fibroblasts and macrophages (Mφ) are key in promoting the formation and remodeling of extracellular matrix (ECM) following organ injury, but aberrant crosstalk can contribute to the development of fibrosis. We hypothesized that mechanically activated MFs control distinct Mφ states in contact dependent signaling processes.

Methods: Mφ were obtained by treating mouse bone marrow-derived monocytes with M-CSF in vitro for 5d. Subcutaneous fibroblasts were isolated from Col1a-GFP reporter mice. Fibroblasts were cultured on skin-soft or scar-stiff gelatin-coated silicone substrates for 2 passages, respectively. Mφ were then co-cultured for 3d with fibroblasts and MFs on the respective substrates in setups that allowed either direct contact or communication restricted to the exchange of soluble factors. Immunofluorescence confocal microscopy and flow cytometry were performed and fibroblastic cells and Mφ were flow-sorted for subsequent RNA sequencing and analysis. Mouse model of full-thickness excision wound+/-splint was established, and tissue samples were collected for selected targets verification.

Results: Fibroblasts cultured alone on stiff substrates exhibit MF protein and RNA profiles absent from soft-cultured fibroblasts. Substrate stiffness in the chosen range does not affect RNA profiles of Mφ in monoculture. Conversely, co-culture with fibroblastic cells results in significant changes in Mφ transcriptomes, with unique features depending both on the activation state of the co-cultured fibroblasts and the ability to form direct contact. Specifically, in direct contact with MFs, Mφ exhibit upregulated pro-fibrotic signaling pathways, mediated by the activation of IL-17, TNF, NF-kB, C-type lectin, and FAT4. Immunofluorescence and flow cytometry analysis validate RNA sequencing data. FAT4 on Mφ is activated in tandem with Dchs1 on fibroblasts, depicting the intercellular crosstalk in profibrotic activation of Mφ.

Conclusion: Direct contact with MFs generate a unique Mφ polarization state that features a combination of proinflammatory and profibrotic signaling which offers novel therapeutic targets for the prevention and treatment of fibrosis.

21 Placenta-on-a-Chip Reveals How Mechanical Pressure Modulates Barrier Function and Trophoblast Differentiation in Placental Dysfunction

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Introduction: Mechanical pressure within the placenta significantly influences pregnancy outcomes and is suspected to contribute to complications such as preeclampsia (PE), intrauterine growth restriction (IUGR), and maternal vascular malperfusion (MVM). However, its direct impact on placental barrier function and trophoblast differentiation remains largely unexplored. Most in vitro placental models neglect mechanical forces, despite their physiological relevance during gestation. As a result, the mechanistic link between elevated pressure and placental pathologies remains poorly understood, highlighting a critical gap in knowledge.

Methodology: We employed a placenta-on-a-chip platform to simulate physiological and pathological pressure conditions (0, 10, 30, and 70 mmHg) on BeWo b30 trophoblast cells cultured with or without forskolin for 72 hours. Forskolin treatment induced differentiation from cytotrophoblasts into syncytiotrophoblasts, enabling comparative analyses between differentiated and undifferentiated cell populations. The secretion profiles of key placental markers—Placental Growth

Factor (PlGF), β-human chorionic gonadotropin (β-hCG), Matrix Metalloproteinase-2 (MMP-2), Transforming Growth Factor-beta1 (TGF-β1), and Interleukin-6 (IL-6), were evaluated via enzyme-linked immunosorbent assays (ELISA).

Results: Mechanical pressure significantly affected trophoblast secretory profiles. PlGF secretion was consistently suppressed under high pressure, with up to ~25% reduction by 72 hours, reflecting angiogenic dysfunction as seen in PE and MVM. β-hCG secretion showed mild reduction early but became more pronounced (~30%) after 72 hours, indicating impaired syncytial differentiation. Cytotrophoblasts (without forskolin) increased MMP-2 secretion at high pressure, suggesting enhanced ECM remodeling, while syncytiotrophoblasts (with forskolin) showed minimal MMP-2 response. Additionally, IL-6 secretion was elevated in syncytiotrophoblasts under sustained pressure, indicating an amplified inflammatory response.

Conclusions: This model demonstrates that mechanical pressure alone alters placental secretory behavior and reveals distinct responses between cytotrophoblasts and syncytiotrophoblasts. It offers a valuable platform to explore the mechanotransduction mechanisms underlying pregnancy complications.

22 Elucidating the role of CXCL1 and CXCL8 in inflammation-induced keratinocyte migration.

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The epidermis, the outer layer of the skin, is primarily composed of keratinocytes. The dysfunction of these cells can lead to chronic inflammation and non-healing wounds. The mechanisms whereby keratinocytes are stimulated during inflammation to produce mediators that promote wound healing remains poorly known. Further, potential autocrine roles of the released mediators are also unknown. To gain new insights, we used a multiplex ELISA to identify main keratinocyte-derived factors. We found that the pro-inflammatory cytokine tumor necrosis factor-alpha (TNFα) increased >35 mediators, including the chemokines CXCL1 and CXCL8. Chemokines are known to affect migration of immune cells, but their effects on keratinocytes remain poorly characterized. My objective is to uncover the molecular mechanisms whereby CXCL1 and 8 release is controlled and establish their role in keratinocyte migration.

Using the immortalized keratinocyte cell line HaCat, I first wished to show the presence of functional receptors for CXCR1/2. CXCL1 and 8 both elevated phosphorylated Erk1/2 by 1.5- and >2-fold, respectively, as demonstrated using western blotting. CXCL1/8 act through the receptors CXCL1 and 2. Indeed, the effect of CXCL1 and 8 on ERK was prevented by Reparixin, a CXCR1/2 inhibitor. Next, I followed HaCat cell migration using live imaging in a gap-closing assay. Cells were grown into a monolayer with a silicone insert to generate a cell-free gap, and migration was induced by removing the insert. CXCL1/8 elevated the rate of migration, and the effect was inhibited by Reparixin. Thus, I have shown that CXCL1/8 induces signaling, and augments keratinocyte migration through CXCR1/2.

My ongoing studies are aimed at demonstrating the mechanisms whereby TNFα augments expression of these chemokines. I will also use silencing to show that they act as autocrine mediators. Since CXCL1/8 are major mediators released under

inflammation, modulating their expression may be beneficial in treating chronic wounds.

23 ResearchWaste.info: Raising awareness of avoidable waste in health research

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Introduction. Health research waste (RW), inefficient or detrimental resource use, was noted by Altman in 1994. Chalmers & Glasziou (2009) estimated RW at 85%; Lancet series (2014) elaborated. A decade later, evidence-based tools to evaluate and decrease RW lack wide implementation. My doctoral research addresses this.

Methodology. Participatory, patient-oriented research, co-led by a patient partner and guided by integrated knowledge translation with omnichannel engagement. Performed to date (Mar 28 '25): 1) Rapid scoping review (ScR) of RW definitions (MEDLINE, Embase from inception to Oct 23 '23; 721 records with "research waste" in title identified, 442 screened, 6 abstracted using predefined methods). 2) Living search (extended search in PubMed, 4163 identified from Dec 22 '23 to date): 2 to 3 new RW studies per week identified via email alerts and screening. 3) Community engagement: ResearchWaste.info (356 unique visits, 185 Canadian); LinkedIn (5,927 impressions). Top sectors: healthcare (23%), research services (16%), higher education (12%). Top locations: Toronto, ON (20%), Copenhagen, Denmark (8%), Vancouver, BC (7%), Victoria, BC (4%). Users: 37% senior career. Face-to-face talks: 60 people (12 faculty/clinicians, 42 trainees, 4 patient and public partners, 2 admin staff), including RW study authors (Lancet '14, MINUS).

Results. Despite the scale and Declaration of Helsinki 2024 mandate, RW is neglected. RW assessment methods are variable, poorly reported, cover limited aspects, and lack comprehensive, user-friendly tools, particularly for patient and public partners.

Conclusions. More research is needed. I propose a mixed-methods study: 1) ScR mapping RW studies/evaluation tools. 2) Key informant interviews/focus groups with researchers, clinicians, patient partners, and other knowledge users, informed by 1. 3) Integrating 1 and 2, develop an accessible interactive web app and pilot it at the Strategy for Patient-Oriented Research Evidence Alliance.

24 The Role of ABO Blood Groups in SARS-CoV-2 Infection

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Abstract: COVID-19, caused by SARS-CoV-2, requires coronavirus Spike (S)-protein, host receptor ACE2 for infection. Emerging progeny virus use host plasma membrane, which may contain ABH(O) antigens, to form envelopes. Multiple studies reported that blood group O protects against severe COVID-19 disease, while group A patients show increased susceptibility. This suggests that anti-A from group O patients could provide natural protection against COVID-19.

ABH-expressing CoV2-Spike (CoV2-S) lentivirus is produced in HEK293T cells by co-transfecting a luciferase-reporter lentiviral vector, ABO/FUT1 glycosyltransferases, and CoV2-S plasmids. The resulting lentivirus is pre-treated with ABO antibodies, then used to infect target cells (HEK293TACE2+), and infection is measured by luciferase read-out. Both IgM and IgG ABO antibodies will be examined as well as a role for complement activation to elucidate the mechanism of inhibition.

ABH expression on immunoprecipitated S-protein from transfected HEK293T has been confirmed and ABH-specific inhibition with IgM-class monoclonal ABO antibodies has been shown in CoV2-S lentivirus. IgM-class anti-A and anti-B specifically inhibited only A- or B-expressing CoV2-S, respectively. Neither antibody inhibited wildtype and H(O)-antigen

expressing CoV2-S. Additionally, pre-COVID-19 plasma from group O, but not group AB, inhibited A- and B-antigen expressing CoV2-S but not H(O)-antigen expressing CoV2-S. IgG-class monoclonal anti-A and anti-B did not inhibit any ABH-expressing or wildtype CoV2-S lentivirus, likely due to lower avidity.

Future work will focus on testing IgG-class polyclonal ABO antibodies in CoV2-S to check if IgG with higher avidity can neutralize the virus. Preliminary work with complement showed it was able to enhance inhibition of IgM anti-A, but not IgM anti-B, which will also be further explored. Additionally, live SARS-CoV-2 will be propagated in ABH-transfected HEK293TACE2+ and tested for ABO-specific inhibition via RT-qPCR and cytopathic effect (CPE). Our study highlights a crucial role of ABO in coronavirus epidemiology, which could aid in managing future outbreaks.

25 Investigating photoacoustic imaging as a novel, radiation-free method for imaging the injured lung

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Abstract: Acute respiratory distress syndromes (ARDS) is a major cause of morbidity and mortality. Excessive lung inflammation, often from pneumonia or sepsis, causes severe pulmonary edema and a reduction in gas exchange, leading to hypoxia and death. Imaging of ARDS relies on chest X-rays/CT scans which possess several limitations: exposure to ionizing radiation, lack of real-time monitoring, lack of physiological information, and (for CT) the requirement for potentially hazardous patient-transport.

To address this problem, we propose the use of photoacoustic imaging (PAI) as a novel lung imaging modality. Briefly, a laser illuminates the lungs and interacts with molecules in tissue (e.g. hemoglobin) to produce an acoustic response which is detected by an ultrasound transducer. Notably, the wavelength of the excitatory laser can be changed to assess different qualities such as oxy- and deoxy-hemoglobin content, providing physiological readouts of lung function. Using a murine pneumonia model, we imaged mice pre- and post-infection to assess the capacity of PAI to measure edematous lung injury. Lungs were collected post-mortem for injury confirmation and PAI images were analyzed to measure oxygen saturation.

Using PAI, we measured changes in acoustic response between healthy and fluid-filled lung tissue. Data from different wavelengths revealed increases in deoxyhemoglobin and decreases in oxyhemoglobin after lung infection. Lung injury was confirmed using histology and wet/dry analysis. Using a scanning apparatus, we generated 3D images of fluid-filled lungs using both ultrasound and photoacoustics, providing a map to identify the most edematous lung regions. Finally, preliminary data from a pig pneumonia model illustrated the feasibility of PAI when scaled up to larger animal models.

Together, these data demonstrate the potential of PAI to provide real-time, radiation-free imaging and physiological monitoring of the injured lung. This disruptive technology has the potential to improve the care of critically ill patients.

26 DialySnake: Safety and Efficacy in Removing Intraluminal Fibrin Plugs in Peritoneal Dialysis Catheters

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

Purpose: We developed the DialySnake, a novel, minimally-invasive tool with the aim of removing IFPs at the bedside, eliminating the need for surgery.

Hypotheses: (1) The DialySnake will prove safe and efficacious in ex vivo testing. (2) Plain X-ray images in the AP view will provide a reliable imaging modality to enable accurate catheter length measurements on photo measure software and ensure DialySnake's safety in removing IFPs in vivo.

Methods: In ex vivo testing, the DialySnake is used to remove IFPs in surgically removed PD catheters post kidney transplantation. In the porcine simulations of an obstructed PD catheter, a 66cm Swan-neck double-cuff Coviden PD catheter was surgically inserted into a pig at St. Michael's Hospital vivarium. Plain X-ray images were taken, and catheter lengths were analyzed using Eleif Photomeasure and Imaios Dicom. Measured lengths were compared to the known catheter length to ensure safe DialySnake insertion, preventing exit beyond the catheter and potential organ damage.

Results: The DialySnake unclogged catheters in a mean of 5 minutes, and there was a strong positive correlation between the length of IFP and number of device passes (r= 0.76). 2/25 and 3/45 measurements exceeded 66cm with Eleif Photomeasure and Imaios Dicom, respectively. 43/45 and 42/45 measurements indicated a safe insertion length for the DialySnake.

Conclusion: The DialySnake is safe and efficacious in removing IFPs ex vivo. Plain AP X-ray is a viable modality to ensure DialySnake's safety and efficacy, offering a cost-effective, minimally invasive alternative to emergency surgery.

27 Investigating oncolytic viruses as a vehicle for delivering CD47 blockade in murine models of lung cancer

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Introduction: CD47 is an immunosuppressive protein exploited by lung cancers (LC) to evade immune destruction. Ligation of CD47 to its receptor SIRPα on dendritic cells and macrophages transmits a potent anti-phagocytic signal that inhibits tumor antigen uptake and cross-presentation, consequently blunting adaptive anti-tumor immunity. Although preclinical evidence indicates that genetic and pharmacologic inhibition of CD47 in LC cells impairs tumor growth in LC models, the efficacy of intravenously administered anti-CD47 therapeutic antibodies (CD47-Abs) has been encumbered by systemic toxicities in clinical trials. This is likely attributable to on-target, off-tumor binding of CD47-Abs to non-malignant cells due to the ubiquitous expression of CD47 on cells throughout the body. Therefore, alternative delivery methods that restrict the effects of CD47 inhibition specifically to lung tumors is imperative to harness the potential of CD47 as an immunotherapeutic target. Here, we aim to develop and evaluate an oncolytic virus (OV)-based approach for therapeutic inhibition of CD47 in LC models.

Methods: We synthesized an attenuated vesicular stomatitis virus encoding a mouse-specific fusion protein (VSV-FP) that blocks CD47 function. Subcutaneous CMT167 tumors grown in immunocompetent mice were treated intratumorally with three doses of PBS, a control OV encoding green-fluorescent protein (VSV-GFP), or VSV-FP (1x106 pfu/dose). Tumor volume and body weights were monitored over the course of treatment to assess the therapeutic effects and tolerability of virotherapy.

Results: OVs were well tolerated in mice as no significant differences in body weight were observed over the course of treatment. VSV-FP elicited stronger tumor growth inhibition than VSV-GFP ($p<0.01$). Notably, VSV-FP abrogated CMT167 tumor growth for 12 days, with 2/8 mice appearing to have near-complete responses.

Conclusions: VSV-FP effectively suppressed lung tumor growth in mice. Our results indicate that OVs can be used to harness the therapeutic potential of CD47 blockade in NSCLC.

28 Evaluating feasibility of a primary-care milk fat recommendation intervention for young children: An internal pilot randomized trial

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Abstract: In Canada, 30% of children and youth develop overweight status or obesity. The Canadian Paediatric Society recommends that children transition from 3.25% fat cow's milk to reduced-fat cow's milk at 2 years of age to reduce child adiposity. However, recent observational research has demonstrated an association between higher fat cow's milk consumption and lower child adiposity, suggesting the need for clinical trials to investigate the effect of cow's milk fat on child adiposity. To develop a well-designed clinical trial, we conducted an internal pilot randomized trial. The objective was to examine the feasibility of a randomized controlled trial (RCT) comparing a primary-care recommendation of 1% or 3.25% cow's milk for 2-year-old children as the intervention by evaluating recruitment, retention, adherence, and age at enrollment. Thirty participants between 1.5 to 2.9 years of age within the TARGet Kids! pediatric cohort were randomized to the Intervention group (3.25% cow's milk recommendation) or Control group (1% cow's milk recommendation). Data was collected through bimonthly email surveys and well-child visits. Feasibility outcomes were assessed using the pre-specified

progression criteria: Green/Feasible (>80%), Amber/Amend (50-80%), and Red/Questionable (<50%) to assess trial feasibility. Outcomes below 80% would prompt improvements to the trial design to enhance the main trial success. Recruitment rate was <50%, with the most common reason for declining participation being a preference for plant-based milks. Adherence to the assigned milk at 6 months was 81% (13/16) for Intervention and 71% (10/14) for Control. Retention at 6 months was 87% (14/16) for Intervention and 86% (12/14) for Control. Child age at enrollment within the range of 1.5 to 2.9 years of age was 87% (14/16) for Intervention and 100% (14/14) for Control. A clinical trial with a primary-care milk fat recommendation as the intervention is feasible. Further qualitative research is required to improve recruitment strategies.

29 VEGF-A and autocrine regulator of keratinocyte migration during skin inflammation.

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Abstract: Keratinocytes play a central role in skin re-epithelialization after injury by proliferating, migrating, and differentiating. They also secrete soluble mediators to initiate inflammation and facilitate skin barrier restoration. However, dysregulated mediator release can lead to persistent inflammation, pathological wound healing, and excessive scarring. The small GTPase RhoA is a key regulator of cell migration, yet the mechanisms governing Rho protein activity in keratinocytes remain poorly understood. This study aimed to investigate the connection between inflammation-induced mediator release and keratinocyte migration, identifying specific RhoA regulators involved in this process. A multiplex cytokine assay was used to quantify mediators secreted by TNFα-stimulated HaCat keratinocytes. Live time-lapse imaging was used to track cell migration. VEGF-activated guanine nucleotide exchange factors (GEFs) were identified through GST-RhoA(G17A) affinity precipitation, followed by mass spectrometry. RhoA and GEF-H1 activation was assessed using affinity precipitation assays. Immunohistochemistry was performed to visualize key proteins in an MC903-induced mouse model of atopic dermatitis (AD). Results show keratinocytes secrete a diverse array of soluble factors, including high levels of Vascular Endothelial Growth Factor (VEGF)-A. TNFα enhanced VEGF-A secretion via SP1, HIF1α, and NFκB. Both TNFα and VEGF-165 significantly promoted keratinocyte migration. Depleting VEGF-A, its receptor (VEGFR2/KDR) or inhibiting RhoA reduced basal migration and abolished TNFα-induced migration. GEF-H1 (ARHGEF2) was identified as a VEGF-A–activated GEF, with activation mediated through KDR and ERK. VEGF-A also promoted GEF-H1 phosphorylation at S886. GEF-H1 depletion impaired VEGF-induced RhoA activation, slowed cell migration, and reduced TNFα-induced VEGF-A release. An AD mouse model showed increased levels of active RhoA, phosphorylated GEF-H1, and phosphorylated KDR in the epidermis. Thus, VEGF-A is a crucial autocrine factor, essential for basal and TNFα-induced keratinocyte migration. VEGF-A activated RhoA through KDR and GEF-H1, this pathway was upregulated in skin inflammation and could be a potential target for future therapeutics for inflammatory skin disease.

30 A Novel Mechanosensitive Factor Regulating Fibroblast Activation

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Background: Activation of mesenchymal progenitors into myofibroblasts after tissue injury is crucial to preserve organ integrity with collagenous scar tissue. However, excessive and persistent production and contraction of extracellular matrix (ECM) can cause pathological fibrosis. Myofibroblasts are activated by injury signals such as TGF-β1 and changes in the mechanical environment (i.e., increasing tissue stiffness). Understanding the mechanisms of myofibroblast activation and persistence is crucial for developing anti-fibrotic therapies.

Rationale: Our lab established silicone culture substrates that imitate the mechanical microenvironment of healthy and fibrotic tissues. Our RNA sequencing data reveal significantly different gene expression of rat MSCs grown on either soft or stiff substrates. Among these genes, the spalt-like transcription factor 1 (Sall1) is highly expressed on soft- but absent in stiff-cultured MSCs, which have a myofibroblast phenotype. However, the mechanisms and functions of Sall1 in mechanically induced myofibroblast activation is unknown.

Methods: Therapeutically relevant human MSCs from the Wharton's jelly of umbilical cords [MSCs (WJ)] were cultured on normal tissue-soft (E modulus=1 kPa) and fibrosis-stiff (100 kPa) substrates to validate our findings with rat MSCs. Quantitative RT-PCR, Western blotting, and immunofluorescence microscopy were used to assess expression and subcellular location of Sall1, and myofibroblast proteins such as α-SMA, collagen, and fibronectin.

Results: Sall1 mRNA and protein are expressed almost exclusively in soft- but not stiff-cultured MSCs(WJ). Profibrotic factor TGF-β1 also inhibited Sall1 on soft-grown MSCs(WJ). Knock-down of Sall1 results in upregulation of the myofibroblast marker α-SMA even in soft-cultured MSCs(WJ). Wilms' tumor 1 (WT1) was found as a downstream target of Sall1, which is downregulated by Sall1 knockdown and upregulated by Sall1 overexpression in MSCs(WJ). WT1 depletion results in myofibroblast activation in soft-cultured MSCs(WJ).

Conclusion: Sall1 acts as a mechanosensitive anti-fibrotic transcription factor through WT1 in soft-cultured MSCs(WJ), which is inhibited by both scar-stiff mechanical microenvironment and TGF-β1.

31 Novel Mechanism of Immune Suppression: Unveiling the Roles of Platelet Desialylation

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Abstract: Platelets are best known for their roles in hemostasis and thrombosis, but emerging evidence highlights their importance as immune modulators. Recent findings from the our lab reveal that desialylated platelets (dPLTs)—formed through aging, chilling, or activation—are uniquely cleared by liver-resident Kupffer cells rather than splenic macrophages. This clearance event initiates a systemic anti-inflammatory response, characterized by increased peripheral regulatory T cells (Tregs) and elevated levels of IL-10 and TGF-β. These results suggest that platelet function is switchable between pro-inflammatory and immune-suppressive roles, and they unveil a novel immune-regulatory axis centered in the liver. This project aims to explore the cellular and molecular mechanisms driving immune tolerance following dPLT clearance, with a focus on how Kupffer cell–T cell interactions shape local and systemic immune responses. Using single-cell RNA sequencing

(scRNA-seq), CITE-seq, and spatial transcriptomics, we will profile transcriptional, protein, and spatial changes in liver immune populations at various time points post-dPLT transfusion. Co-culture assays will further dissect how dPLTs modulate Kupffer cell phenotype and T cell differentiation, including Treg, T follicular helper (Tfh), and Th1/Th2 subsets. To assess therapeutic relevance, dPLTs will be tested in murine models of immune thrombocytopenia (ITP) and atherosclerosis. These models will evaluate whether dPLTs can restore immune balance and reduce pathological inflammation. Real-time intravital microscopy will be employed to visualize dPLT clearance and immune cell interactions within the liver. This research may define a novel, easily implementable strategy for inducing immune tolerance, with potential applications in autoimmune disease, transplantation, and inflammation-related disorders. As dPLTs can be readily generated by chilling, they represent a low-cost and translatable therapeutic platform. Ultimately, these findings could inform precision immunotherapies and advance our understanding of liver-driven immune regulation.

32 Novel Cancer Therapy: Targeting Integrin β3 PSI Domain to Simultaneously Impede Cancer Metastasis and Cancer-Associated Thrombosis

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Background: Widespread metastases and Cancer-Associated Thrombosis (CAT) represent the two leading causes of death for cancer patients. Platelets are prominent contributors to tumor metastasis and CAT via synergistic, bidirectional communication. A common denominator on cancer cells and platelets is integrin β3; present primarily in the form of αVβ3 and αIIbβ3 on tumor cells and platelets, respectively. The PSI domain of subunit β3 demonstrates endogenous thiol-isomerase activity contributing to integrin activation and function. However, the role of integrin β3 PSI domain activity in tumour metastasis and CAT has never been explored.

Methods/Results: In this study, we discovered that inhibiting integrin β3 PSI domain with monoclonal antibody PSI E1 reduced spontaneous pulmonary metastasis of cell line 4T1 in orthotopic models of wild type (WT) and thrombocytopenic BALB/c mice, but not β3-/- mice, determined through quantification of metastatic area from HE stains of cryosectioned lung tissue. Additionally, there was decreased metastasis in the untreated 4T1 thrombocytopenia and β3-/- mice compared to WT, suggesting platelet-mediated and possibly platelet-independent effects. Treatment did not abate primary tumor growth in either of these models. Macroscopic observation of lungs retrieved from WT mice bearing 4T1 tumours appeared to have thrombotic events, which was supported by histological staining of fibrin and erythrocytes, that were reduced in the PSI E1-treated cohort. Furthermore, anti-PSI-treated mice exhibited reduced vessel occlusion. Immunofluorescence staining and 3D reconstruction of platelet aggregates in lung cryosections from mice 1 hour after injection with labeled cancer cells revealed a higher ratio of single platelets to platelet aggregates in anti-PSI-treated mice. Importantly, anti-integrin β3 PSI treatment inhibited cancer cell-induced platelet fibrinogen binding, which suggests disruption of a classical mediator for cancer-platelet interaction and a necessary element of CAT.

Conclusions: Inhibiting the PSI Domain of Integrin β3 impairs cancer metastasis and cancer-associated thrombosis possibly through inhibiting cancer-platelet crosstalk.

33 Shared Genetic Risk in Autoimmune and Inflammatory Diseases

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Abstract: Autoimmune and inflammatory diseases (AID) are characterized by chronic inflammation and reactivity to self-antigens. AID frequently co-occur in families and individuals with one AID are more likely to develop a second when compared to the average individual. These observations suggest shared risk factors and disease mechanisms. Genome wide association studies (GWAS) have identified hundreds of genetic risk loci for AIDs, though resolution is limited and we do not know the precise causal variant that drives risk for most loci. Limited GWAS resolution is fundamentally a problem of sample size; as most available disease cohorts have already been studied, resolution improvements would require costly recruitment of new subjects.
We aim to improve genetic resolution for AID by taking advantage of shared genetic mechanisms among these diseases. In a previous study, we identified overlapping genetic associations among 6 AIDs. By using joint likelihood mapping (JLIM), we identified instances where the same causal variant drove risk for multiple diseases. By combining data across diseases at shared genetic risk loci, we doubled genetic resolution for shared loci.
We are now expanding this study to a collection of 19 AIDs for which we have GWAS summary statistics. After data harmonization and quality control filtering, we used PLINK to define loci of interest in each dataset. We used conditional joint analysis (COJO) to allow for multiple independent genetic effects in each locus. We have identified overlapping genetic loci, and we will use JLIM to determine which of these have the same underlying effect. For each set of overlapping loci that are the same effect, we will combine the results in a meta-analysis and use fine-mapping techniques to quantify resolution. In this way, we will identify variants most likely to be causal for each disease for further research into the mechanism of disease.

34 How to keep myofibroblasts under control: culture of mouse skin fibroblasts on soft substrates

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"How to keep myofibroblasts under control: culture of mouse skin fibroblasts on soft substrates

Abstract: During the physiological healing of skin wounds, fibroblasts recruited from the uninjured adjacent dermis and deeper subcutaneous fascia layers are transiently activated into myofibroblasts to first secrete and then contract collagen-rich extracellular matrix into a mechanically resistant scar. Scar tissue restores skin integrity after damage but comes at the expense of poor esthetics and loss of tissue function. Stiff scar matrix also mechanically activates various precursor cells into myofibroblasts in a positive feedback loop. Persistent myofibroblast activation results in pathological accumulation of fibrous collagen and hypertrophic scarring, called fibrosis. Consequently, the mechanisms of fibroblast-to-myofibroblast activation and persistence are studied to develop anti-fibrotic and pro-healing treatments. Mechanistic understanding often starts in a plastic cell culture dish. This can be problematic because contact of fibroblasts with tissue culture plastic or glass surfaces invariably generates myofibroblast phenotypes in standard culture. We adapted a straight-forward method to produce 'soft' cell culture surfaces for fibroblast isolation and continued culture by adding a layer of elastic silicone polymer tunable to the softness of normal skin. In addition to the stiffness regulation, treatment of TGF-beta1 or modification of cell seeding density was tested to regulate the fibroblast-to-myofibroblast activation. Expression of alpha-smooth muscle actin (alpha-SMA), a marker of myofibroblast, was increased with stiffness, TGF-

beta1, seeding density and passaging. Employing soft stiffness or its combination with cytokine or seeding density regulation can help to control fibroblast mechanotransduction and downstream activation into myofibroblasts.

35 Exploring the Association of Neuropsychiatric Symptoms with Blood-Based Biomarkers in Alzheimer's Disease and Mild Cognitive Impairment

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Background: Neuropsychiatric Symptoms (NPS) may be present in individuals with Alzheimer's Disease (AD), worsening their overall symptom burden. This study explores the association between NPS scores and blood-based biomarkers implicated in AD including Glial Fibrillary Acidic Protein (GFAP), Neurofilament Light Chain (NFL), Amyloid Beta (AB40 and AB42), and Phosphorylated Tau at Threonine 181 (pTAU181).

Methods: Data from the ONDRI database was used to conduct this study. Individuals with a diagnosis of Alzheimer's Disease or Mild Cognitive Impairment were included in the analysis (N=126), wherein 107 had a complete Neuropsychiatric Inventory Questionnaire (NPI-Q) and provided blood samples for measurement of the biomarkers. A partial Spearman correlation was conducted (N=107); adjusting for age, sex, and education level. A False Discovery Rate (FDR) threshold of 0.05 was applied to all p-values to control for multiple comparisons.

Results: Apathy scores had a significant positive correlation with pTAU181 ($R_s = 0.27$, $p = 0.04$) and NFL plasma levels ($R_s = 0.30$, $p = 0.02$); Anxiety scores showed a significant positive correlation with GFAP ($R_s = 0.28$, $p = 0.03$) and NFL plasma levels ($R_s = 0.33$, $p = 0.006$); Euphoria scores were positively correlated with NFL plasma levels ($R_s = 0.27$, $p = 0.05$); Appetite, Motor function, and Total NPI severity scores had a significant positive correlation with GFAP plasma levels ($R_s = 0.31$, $p = 0.01$; $R_s = 0.31$, $p = 0.01$; $R_s = 0.29$, $p = 0.03$). No significant findings were observed for AB40 and 42 with any NPS domain.

Discussion: Our findings suggest that pTAU181, NFL, and GFAP are associated with the presence of NPS in Alzheimer's Disease. These biomarkers could provide insights into the underlying mechanisms and track the severity of NPS. However, additional research with larger sample sizes and longitudinal studies is required to validate these results and investigate causal links.