Summer Student Research Day

August 13, 2019
Cruess Amphitheatre & Elspeth McConnell Atrium
Dear Summer Research Students,

Congratulations! We are delighted to celebrate the successful completion of your time as a summer research trainee here at the RI-MUHC. Over the past several months you have learned how to follow your curiosity, ask scientific questions and understand how to answer them. So today is an opportunity to recognize these skills and welcome you into our research community. In addition to your work, you will have the chance to experience the quality, breadth and complementarity of the research taking place at this institution by engaging with the efforts of other summer research students. Take the time to listen to the oral presentations and visit the posters of your colleagues – these open exchanges of ideas are the foundations of building a career in science. We hope that what you have learned during your time with us has enriched your understanding of the research environment and inspired your plans and studies for the future.

Thank you for your enthusiasm and hard work, and for being a part of the RI-MUHC this summer.

With sincere appreciation,

Your Program Managers

Dear Summer Students,

The Desjardins Centre for Advanced Training team wants to congratulate you on your achievements this summer. For those that participated in our Summer Student Weekly Workshops, we hope that you found these to be a springboard for your continued success in research. Your enthusiasm for research is evident and we encourage you to keep exploring all the possibilities open to you for a fulfilling and exciting career in science and research.

New career paths for those trained in science are opening up every day. We hope that you will consider DCAT and the RI-MUHC as a partner for your future career development. If you have questions about your career, feel free to contact us for an informal chat.

Congratulations on all your successes!

The Desjardins Centre for Advanced Training Team
AGENDA

8:30 Registration

8:55 Welcoming remarks

9:00 Oral Presentations — Session 1

10:20 Coffee break

10:50 Oral Presentations — Session 2

12:00 Oral presentation closing remarks

12:10 Lunch break
   Lunch is provided for presenting summer students and a supervisor (PI or senior trainee)
   All posters need to be on their boards by 12pm!

13:00 Poster Session
   All presenters must be by their poster

13:30 Poster Pitch session, per group (A-G)

14:30 Closing remarks and prize presentations
   Please remove your poster from the board!
<table>
<thead>
<tr>
<th>Time</th>
<th>Presenter</th>
<th>Supervising PI</th>
<th>Program</th>
<th>Title</th>
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<tbody>
<tr>
<td>9:00</td>
<td>Amy Zhou</td>
<td>K. Murai</td>
<td>BRaIN</td>
<td>A closer look into the diseased brain: discovering the ultrastructure of astrocytes in the Alzheimer’s model</td>
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<tr>
<td>9:10</td>
<td>Kaveh Gaynor-Sodeifi</td>
<td>D. Jensen</td>
<td>RESP</td>
<td>Associations between Fat Free Mass and Exercise Physiological and Perceptual Outcomes in People with Chronic Obstructive Pulmonary Disease: A Research Project Proposal</td>
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<tr>
<td>9:30</td>
<td>Adam Ptack</td>
<td>N. Jabado</td>
<td>CHHD</td>
<td>Characterizing differences in phenotypes of histone mutations in the epigenome and broader cell contexts</td>
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<tr>
<td>9:40</td>
<td>Ida Derish</td>
<td>E. Torban</td>
<td>MeDiC</td>
<td>Differential role of core planar cell polarity gene Vangl2 in murine embryonic and postnatal renal tubules</td>
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<tr>
<td>9:50</td>
<td>Carla Benea</td>
<td>N. Dayan</td>
<td>CHAL</td>
<td>Feasibility of self-efficacy based breastfeeding intervention in mothers with recent hypertensive complications of pregnancy</td>
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<tr>
<td>10:00</td>
<td>Laura Widawski</td>
<td>C. Piccirillo</td>
<td>IDIGH</td>
<td>Phenotypic and Functional Characterization of Four IPEX Mutations in the human FOXP3 gene</td>
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<tr>
<td>10:10</td>
<td>Céline Tilliet</td>
<td>G. Merle</td>
<td>IRR</td>
<td>Biodegradable nanomaterials for implantable glucose oxygen biofuel cells</td>
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## Oral Presentations — Session 2

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<tr>
<td>10:40</td>
<td>Emily Chen</td>
<td>JG. Martin</td>
<td>RESP</td>
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<td></td>
<td>Characterizing the Effects of Chlorine-induced Airway Injury on Endoplasmic Reticulum Stress in a Murine Model</td>
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<td>10:50</td>
<td>Amina Medyouf</td>
<td>P. Goodyer</td>
<td>CHHD</td>
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<td></td>
<td>Effect of aminoglycoside derivative, ELX-02, on CTNS non-channel function in proximal tubule cells</td>
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<td>11:00</td>
<td>Yulia Alexandrova</td>
<td>C. Costiniuk</td>
<td>IDIGH</td>
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<td></td>
<td>Functional assay of CD8 T-cells in bronchoalveolar lavage fluid and peripheral blood in persons living with HIV on suppressive antiretroviral therapy</td>
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<td>11:10</td>
<td>Victoria Montgomery</td>
<td>W. Kassouf</td>
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<td></td>
<td>Murine Bladder Cancer Organoids</td>
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<td>11:20</td>
<td>Parmoon B. Sarmadi</td>
<td>D. Rosenzweig</td>
<td>IRR</td>
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<td></td>
<td>The effects of 17ß-estradiol &amp; progesterone treatments on ligament regeneration</td>
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<td>11:30</td>
<td>Julia Rodighiero</td>
<td>J. Afilalo</td>
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<td></td>
<td>Restricted Mean Survival Time of Older Adults Referred For But Not Undergoing Transcatheter Aortic Valve Replacement</td>
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<td>11:40</td>
<td>Abigail McLellan</td>
<td>R. Farivar</td>
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<td>Transcranial Magnetic Stimulation In The Primary Visual Cortex</td>
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<td>11:50</td>
<td>Yoojung Kim</td>
<td>D. Goltzman</td>
<td>MeDiC</td>
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<td></td>
<td>Parathyroid Cell Transcription Factor Glial Cells Missing-2: Novel Inactivating and Activating Mutations Associated with Hypoparathyroidism and Hyperparathyroidism, Respectively</td>
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**Poster Session**

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<tr>
<td>A-1 Selen Ay</td>
<td>I. Gupta</td>
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<td>The role of folate insufficiency and excess during kidney and urinary tract development</td>
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<td>A-2 Parmoon B. Sarmadi</td>
<td>D. Rosenzweig</td>
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<td>Highly porous elastomer scaffolds for the ligament and cartilage tissue engineering</td>
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<td>A-3 Stacey Beard</td>
<td>J. Kildea</td>
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<td>Patient-Powered Research Using the Multi-Institutional Opal Patient Portal</td>
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<td>A-4 Alaina Bui</td>
<td>S. Enger</td>
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<td>Calculating the G-value for hydrated electrons using Geant4-based simulation</td>
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<td>A-5 Sandrine Busque</td>
<td>S. Rousseau</td>
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<td>The impact of estrogen on cytokine synthesis by bronchial airway epithelial cells infected with Pseudomonas aeruginosa</td>
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<td>A-6 Briana Cabral</td>
<td>J. Kildea</td>
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<td>Opal, the Patient Portal: Pilot Release and Beyond</td>
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<td>A-7 Connor Castrataro</td>
<td>N. Braverman</td>
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<td>Longitudinal Natural History Study of Peroxisome Biogenesis Disorders in the Zellweger Spectrum: Management Guidelines for Adolescent and Adult Patients</td>
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<td>A-8 Tomer Jordi Chaffer</td>
<td>S. Hussain</td>
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<td>Parkin Overexpression Attenuates Muscle Atrophy and Rescues Mitochondrial Morphology in Sepsis-Induced Skeletal Muscle Dysfunction</td>
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<td>B-9 Kim Chagnon</td>
<td>M. Lavoie-Tremblay</td>
<td>BRaIN</td>
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<td>Models to engage children as patient-partners: A scoping review</td>
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<td>B-10 Ethan Chen</td>
<td>T. Takano / S. Lemay</td>
<td>MeDiC</td>
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<td>The adapter protein Dok-4 binds to Rho GTPase-activating proteins (GAPs) in a tyrosine kinase-regulated manner through its PTB domain</td>
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<td>B-11 Yunxi Chen</td>
<td>J. V. Burnier</td>
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<td>The role of cancer-stem cells in malignant melanoma</td>
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<td>B-12 Tessa Condon</td>
<td>J. Kildea</td>
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<td>Waiting Time Visualizations for Patient Appointments in the Opal Patient Portal</td>
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<td><strong>B-13</strong> Sabrina C. Maldonado</td>
<td>S. A. Enger</td>
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<td>Identification of tumor and healthy regions on biopsy slides by using machine learning algorithms</td>
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<td><strong>B-14</strong> Stephanie Deng</td>
<td>C. Rocheleau</td>
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<td>Characterization of the role of ALFA-1 in C. elegans vulva induction and epidermal growth factor signaling</td>
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<td><strong>B-15</strong> Diana Di Iorio</td>
<td>S. Daskalopoulou</td>
<td>CHAL</td>
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<td>The role of sex hormones in plaque instability in men and women with severe carotid atherosclerosis</td>
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<td><strong>B-16</strong> Marianne Dufresne</td>
<td>A. K. Ryan</td>
<td>CHHD</td>
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<td>A Characterization of Abnormal Growths of the Neural Ectoderm in C-CPE-Treated Chick Embryos</td>
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<td><strong>C-17</strong> Camila Etchart</td>
<td>J. Mitchell / F. El Turk</td>
<td>CHHD</td>
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<td>Identifying clinical biomarkers for Mucopolysaccharidoses through analysis of serum cytokine, GAGs, and ceramide profiles</td>
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<td><strong>C-18</strong> Leila Feng</td>
<td>P. Tonin</td>
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<td>Genetic analysis of a RECQL variant c.1138A&gt;T [p.Lys380*] in French Canadian breast cancer cases with familial breast cancer</td>
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<td><strong>C-19</strong> Romina Filippelli</td>
<td>T. Nilsson</td>
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<td>Involvement of Arf1/COPI Machinery on Lipid Droplet Dynamics</td>
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<td><strong>C-20</strong> Marc-Antoine Fortin</td>
<td>I. Levesque</td>
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<td>Shape recognition in perfusion MRI as an early marker of treatment response in breast cancer</td>
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<td><strong>C-21</strong> Myriam Harbec</td>
<td>D. Labbé</td>
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<td>Investigating the high fat diet-induced deregulation of DNA damage response in MYC-driven prostate cancer</td>
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<td><strong>C-22</strong> Orfeo Harrisson</td>
<td>J. Mitchell/F. El Turk</td>
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<td>Biomarkers for Mucopolysaccharidoses</td>
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<td><strong>C-23</strong> Salomé Henry</td>
<td>A. Daftary</td>
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<td>Standardized Patients: An Approach to Understanding the Realities of the Health Care Cascade in Kwazulu Natal and Gauteng</td>
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<td>C-24 Cedric Hupperetz</td>
<td>D. Nguyen</td>
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<td><em>The Role of las Quorum Sensing on the Interactions of Intracellular Pseudomonas aeruginosa and Airway Epithelial Cells</em></td>
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<td>D-25 Meera Kanagalingham</td>
<td>J. Kildea</td>
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<td><em>An analysis of the anatomical changes of the rectum and bladder in prostate cancer patients over the course of radiation therapy</em></td>
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<td>D-26 John Kaoumi</td>
<td>S. Daniel</td>
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<td><em>Primary stability measures of bone anchored hearing implants installed in human cadaveric bones</em></td>
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<td>D-27 Emina Kubat</td>
<td>M. Divangahi</td>
<td>RESP</td>
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<td><em>Ontogeny of macrophages dictate a unique metabolic profile with a distinguished anti-viral immunity against IAV infection</em></td>
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<td>D-28 Claire Lawson</td>
<td>S. Chevalier</td>
<td>MeDiC</td>
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<td><em>Analyzing Muscle Loss and Myosteatosis after Surgical Prehabilitation in Lung Cancer Patients</em></td>
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<td>D-29 Clara Lloyd</td>
<td>M. Srour</td>
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<td><em>Testing for the involvement of GIT1, GIT2, ARF1 and ARF6 in Congenital Mirror Movement Disorder</em></td>
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<td>D-30 Maria Agustina L. Laporte</td>
<td>N. Dayan</td>
<td>CHAL</td>
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<td><em>Maternal ICU admissions at the MUHC and Impact of Advanced Maternal Age on Outcomes: Retrospective Chart Review</em></td>
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<td>D-31 Julia Macintosh</td>
<td>S. Rousseau</td>
<td>RESP</td>
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<tr>
<td><em>Establishing a model of Pseudomonas aeruginosa infection in zebrafish larvae</em></td>
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<td>E-32 Nabil Nathoo-Khedri</td>
<td>S. Daniel</td>
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<td><em>Assessing skin tolerability scales of percutaneous bone-anchored hearing implants using the Holgers classification, IPS, and Tullamore scales</em></td>
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<td>E-33 Hyejin Park</td>
<td>N. Kronfli</td>
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<td><em>Examining HIV transmission clusters among newly-diagnosed asylum seekers in Montreal, Quebec</em></td>
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<td>E-34 Jessica Pei</td>
<td>A. Gregorieff</td>
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<td><em>The Role of Myofibroblast in Infection and Inflammation</em></td>
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<td><strong>E-35</strong> Jeffrey Qin</td>
<td>V. Sangwan</td>
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<td>Role of Neutrophils in Cancer</td>
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<td><strong>E-36</strong> Sarah Randall</td>
<td>J. Kildea</td>
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<td>User interface redesign of the Opal patient portal app to allow informal caregivers to view patient data</td>
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<td><strong>E-37</strong> Zakaria Ratemi</td>
<td>C. Rocheleau</td>
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<td>Investigating the function of Rab18 in regulating cytosolic lipid droplet storage in C. elegans</td>
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<td><strong>E-38</strong> Arrchsana Ratnarajah</td>
<td>M. Lavoie-Tremblay</td>
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<td>The use of artificial intelligence in detecting sepsis in acute care patients and its clinical implications: A systematic review</td>
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<td><strong>F-39</strong> Erfan Sadri</td>
<td>J. Genest</td>
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<td>FHCanada Registry: our national registry for patients with familial hypercholesterolemia</td>
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<td><strong>F-40</strong> Monica Salas</td>
<td>M. Brossard-Racine</td>
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<td>Brain Metabolic Profile of Youths Born with CHD</td>
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<td><strong>F-41</strong> Patrick Samaha</td>
<td>G. Sebastiani</td>
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<td>De novo and recurrent nonalcoholic steatohepatitis after liver transplantation: a prospective study employing cytokeratin 18 and transient elastography</td>
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<td><strong>F-42</strong> Joseph Sayegh</td>
<td>S. Daniel</td>
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<td>A systematic review and an athymic nude mouse model evaluating treatment modalities of keloid scars</td>
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<td><strong>F-43</strong> Matheus Schultz</td>
<td>T. Nilsson</td>
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<td>Assessing the effects of TPD52 on cell growth inhibition by oleate</td>
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<td><strong>F-44</strong> Michelle Shen</td>
<td>D. Labbé</td>
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<td>Mechanisms of High-Fat Diet-Induced DNA Damage Repair in Prostate Cancer</td>
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<td><strong>F-45</strong> Tamara Sogomonian</td>
<td>E. Torban</td>
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<td>Fuzzy +/- induces downregulation of key pathways involved in embryonic renal development</td>
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<tr>
<td>G-46 Emily Tam</td>
<td>C. Polychronakos</td>
<td>CHHD</td>
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<td></td>
<td><em>Genetic Studies on Monogenic Diabetes</em></td>
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<td>G-47 Anaïs Vertueux</td>
<td>A. Ryan</td>
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<td><em>The pattern of claudin 3 and 8 at the boundary between the neural and non neural ectoderm</em></td>
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<td>G-48 Zoe Verzani</td>
<td>S. Daniel</td>
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<td><em>Smoking as a risk factor for spontaneous bone anchored hearing implant extrusion</em></td>
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<td>G-49 Catherine Wang</td>
<td>I. Gupta</td>
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<td><em>The removal of claudins in embryonic mouse submandibular gland explants results in abnormal branching morphogenesis</em></td>
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<td>G-50 Yifei Wang</td>
<td>S. Wing</td>
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<td><em>Targeting the Misfolding-Associated Protein Secretion pathway to hinder the progression of Parkinson’s disease</em></td>
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<td>G-51 Yuxuan Wang</td>
<td>D. Labbé</td>
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<td><em>Diet-dependent immune infiltration in murine prostate cancer models</em></td>
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<td>G-52 Mariya Yordanova</td>
<td>M. Zappitelli</td>
<td>CHHD</td>
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<td><em>Evaluation of Kidney and Blood Pressure Outcomes 11 Years Following Acute Kidney Injury in Critically Ill Children</em></td>
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Oral Presentations — Abstracts
A closer look into the diseased brain: discovering the ultrastructure of astrocytes in the Alzheimer’s model

Amy Zhou1, Alexandra L. Schober1, J. Benjamin Kacerovsky1, Christopher Salmon1, Nensi Alivodej1, Keith K. Murai1

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Astrocytes are highly complex cells that are crucial in the maintenance of brain function. Their morphology is closely tied with their major role in supporting neurons by providing nutrients, buffering of ions and neurotransmitters, and controlling synapse function. Recently, astrocytes have been implicated to play a major role in neurodegenerative disorders such as Alzheimer’s disease (AD). Much research is focused on the functional aspect of astrocytes in the AD brain, but the morphological changes these cells undergo during AD is profound and not well understood. To better understand the morphology of astrocytes in both healthy and AD mice, we looked at both ultrastructure and topographical features in astrocytes (including subcellular organelles and metabolic substrates) of mice from the double transgenic APP/PS1 background. We used focused ion beam serial electron microscopy (FIB-SEM) to image an 8-10mm block of tissue from layer 2/3 of the barrel cortex. These images were first analysed on ImageJ using the TrakEM2 plugin which allows for 2D manual tracing of astrocyte features. The traced images were then transformed into a 3D structure using Blender. Quantitative data was acquired through MATLAB 3D volumetric image processing and novel image analysis using python language. With these tools, we were able to measure curvature, thickness, and surface to volume ratio of the AD astrocyte and compared these measurements with a healthy control. In order to observe changes in intracellular features such as organelles and metabolic substrates, machine learning is being implemented using Ilastik. Ilastik’s Pixel Classification can identify unique objects within 2D images and perform automated tracing. We propose using Ilastik to successfully identify mitochondria and glycogen granules. Using this data, we can identify morphological changes in mitochondria (energy producing organelle), and alterations in glycogen granule (energy substrate) distribution. The data provided by these imaging techniques provide an important structural framework for understanding how astrocyte morphology is changed during AD and how this may relate to both normal and abnormal brain function.
Associations between Fat Free Mass and Exercise Physiological and Perceptual Outcomes in People with Chronic Obstructive Pulmonary Disease: A Research Project Proposal

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Background: Body Composition, specifically fat-free mass (FFM), has been a parameter of growing interest to researchers within the chronic obstructive pulmonary disease (COPD) community, with loss of FFM commonly observed in people with COPD. The loss of FFM has been established as an independent predictor of adverse health outcomes in COPD, including premature death. However, there is limited research on the association between COPD-related alterations in FFM and physiological and/or perceptual responses that occur during a cardiopulmonary exercise test (CPET) in this patient population. Therefore, while there’s an established link between FFM and adverse health outcomes in COPD, little is known about the underlying physiological and/or perceptual mechanisms that lead to poor health outcomes and how this is related to FFM.

Objective: This study aims to answer four research questions in people with COPD:

Methods: To address the first research question, a systematic literature review will be conducted. Studies will be included in the review if they measured FFM and report associations with patient-reported and/or clinical outcomes in people with COPD. Findings will be summarised descriptively and quantitatively, where data permits. The second question will be addressed with a retrospective analysis of cross-sectional data from 60 COPD patients with paired DEXA and incremental CPET data. The third and fourth questions will be addressed by retrospectively analyzing data from a longitudinal intervention-based study in 45 COPD patients. Specifically, this analysis will examine the effect of an 8-12 week RET program on DEXA-derived FFM and scrutinize the association of these changes in FFM with corresponding changes in physiological and perceptual responses to constant-load CPET.

Anticipated results: We anticipate that the systematic review will support associations between FFM and patient-reported and clinical outcomes, with few studies identified that specifically explore associations between FFM and CPET responses. We hypothesize that the retrospective analyses will identify positive associations between DEXA-derived FFM and CPET responses, which are amendable to a RET intervention.
Characterizing COX-2-associated gene network in triple negative breast cancer: its role in distant metastasis and COX-2 inhibitor resistance

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Background: TNBCs account for 15 to 20% of all breast cancers and are characterized by the lack of expression of estrogen, progesterone receptors and human epidermal growth factor receptor 2 (HER2). Due to the lack of specific targets for this type of tumors, there are currently no available efficient treatments for TNBCs. We recently found cyclooxygenase-2 (COX-2) to be highly expressed in TNBC patients and its expression to correlate with poor overall and metastasis free survival outcomes in basal breast cancer. We also found COX-2 to induce breast cancer self-renewal, indicating COX-2 as a promising therapeutic target for TNBC. Clinical trials, on the other hand, reported mixed results on the use of COX-2 inhibitors for breast cancer treatment as patient responses vary. Therefore, there is an urgent need to elucidate the mechanisms underlying the role of COX-2 and associated genes in mediating COX-2 inhibitor response.

Methods/Results: In silico analysis of human breast cancer RNA-sequencing data was performed to identify gene expression patterns associated with COX-2 in TNBCs. Publically available datasets with mRNA, genomics, and clinical outcome were interrogated to identify 10 COX-2-associated genes (GL1-10) that are amplified and highly expressed in aggressive BCs and COX-2-inhibitor-resistance cell lines and that are associated with poor BC patient outcomes. We hypothesize these genes will not only promote TNBC tumor progression, but also contribute to BC resistance to COX-2 inhibitors. Currently, function validation including in vitro cell viability assay and in vivo tumor metastasis experiments are underway in two TNBC-derived cell lines (SUM159 and MDA-MB-231).

Conclusion: The combined in silico, in vivo, and in vitro analysis provides a systematic screening of COX-2-associated genes that 1)- have parallel functions to COX-2 in promoting tumorigenesis, especially metastasis and 2)- regulate breast tumor resistance to COX-2 inhibitors. These findings will be helpful for developing combination therapies for cancer patients with different responses to COX-2 inhibitors.
Characterizing differences in phenotypes of histone mutations in the epigenome and broader cell contexts

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Cancer is the leading cause of disease-related death among children. Several cancers, both adult and pediatric, result in part from mutations in histone proteins. These oncohistones can lead to numerous different diagnoses which can have remarkably different characteristics. K36M is commonly present in adult chondroblastoma along with head and neck squamous cell carcinoma; G34R and G34V are commonly found in pediatric cortical glioblastoma; G34W and G34L in giant cell tumors of bone (GCT); and K27M in pediatric midline glioblastoma, an aggressive and devastating high-grade glioma. Studies have shown that these mutations have an effect on the methylation of K27 and K36. Recent research has suggested that these mutations also affect the differentiation from stem cells into various progenitor cells and into their final, specialized cell. This study will attempt to use the CRISPR cas 9 system to introduce these six mutations into a line of induced pluripotent stem cells (iPSC) and a line of human embryonic stem cells (hESC). This system will permit the comparison of the phenotypes caused by the mutations. ChIP-Seq will be used to compare the trimethylation of K27 and K36 between the oncohistones. These cells will then be differentiated into neural progenitor cells (NPC) and mesenchymal progenitor cells (MPC), the presumed precursor cells for any of the tumors caused by the studied mutations. Immunofluorescence will be performed on all progenitor cells for NPC lineage markers such as Nestin and SOX2, as well as MPC lineage markers such as CD90 and CD105 to observe the ability of the cells to differentiate into both NPCs and MPCs. These cells can be used to generate a brain organoid which can allow the study of their heterozygosity using single cell RNA sequencing. Once these experiments are completed, the results may aid in the discovery of mechanism behind the formation of these tumours. Understanding the mechanism could allow researchers to develop specific drugs and other targeted treatments that could be more effective than current options.
Differential role of core planar cell polarity gene Vangl2 in murine embryonic and postnatal renal tubules

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Congenital anomalies of the kidney and urinary tract (CAKUT) are a subset of abnormalities which represent approximately 20%-30% of all prenatally identified malformations. CAKUT encompasses inherited disorders such as polycystic kidney disease (PKD), characterized by the formation and progressive enlargement of renal cysts. Defective planar cell polarity (PCP) was postulated to cause PKD, although the mechanisms have yet to be elucidated. The transmembrane protein encoded by the Van Gogh-like 2 (Vangl2) gene is a key component of the PCP pathway and its mutation has been strongly linked with a cystic phenotype. Data from our lab previously demonstrated that ubiquitous and conditional excision of Vangl2 led to tubular dilatation and cyst formation during embryonic kidney development, via the disruption of PCP-mediated processes. The goal of this project was to determine whether dysregulated PCP in postnatal tissues also resulted in tubular dilatation. Conditional mutant mice were compared to age-matched controls, with postnatal age being varied parametrically as follows: 1-day (P1), 7-days (P7), 1-month (P30), 3-months (P90), 6-months (P180) and 9-months (P270). Conditional excision was confirmed through Western blotting and anti-Vangl2 immunostaining. Mouse kidney sections were immunostained to visualize collecting ducts, and images of circular collecting duct tubules were acquired through fluorescence microscopy. The cross-sectional area and the cell count per tubule were measured. Analysis of conditional mutant P1 tissues showed that the upper quartile subset of tubules had a significantly increased area and higher number of nuclei per cross-section, compared to controls (p<0.05). Hematoxylin and eosin (H&E) staining confirmed the presence of rare cortical cysts in P1 sections. Surprisingly, quantitative analysis of tissues at later stages revealed no statistical difference between groups, for area and cell count. Morphological assessment of H&E-stained postnatal tissues at the cortical and pelvic regions of the kidney exhibited a normal phenotype. Collectively, our data suggest that the loss of Vangl2 does not lead to tubular widening after birth, contrasting with our findings of significant tubular dilatation following Vangl2’s excision in mouse embryos. The disruption of PCP seems to have no effect on the development of a cystic phenotype postnatally, since the loss of the Vangl2 gene is insufficient for cyst formation. We conclude that while the PCP pathway controls embryonic renal tubular development, its role in tubular maintenance seems to attenuate soon after birth. We hypothesize that a mechanistic switch might take place, and defects in additional pathways are required for the manifestation of a cystic phenotype.
Feasibility of self-efficacy based breastfeeding intervention in mothers with recent hypertensive complications of pregnancy

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Background: Hypertensive diseases of pregnancy (HDP) put women at risk of cardiovascular health problems later in life since they have been shown to increase the risk of chronic hypertension and ischemic heart diseases by 2- to 3-fold in women 10-15 years after delivery. Exclusive breastfeeding is advised for at least 6 months for infant well-being by the WHO, yet most Canadian mothers do not reach this recommendation. Since breastfeeding has been shown to lower blood pressure short and long term and to lower the risk for later cardiovascular diseases, and since women with HDP are vulnerable to early weaning, it is important to assess the effectiveness of a self-efficacy based breastfeeding intervention, shown to be effective in healthy women, in this high-risk population. In fact, observational data has shown that women that have had HDP who breastfed for more than 6 months, compared to those that didn’t, had reduced blood pressure. However there exists no randomized trials, reason for which a pilot feasibility study of a self-efficacy based breastfeeding intervention is needed.

Objective: To certify feasibility, refusal rate will be ≤ 50%, drop-out rate at the first follow-up will be <20%, missing data rate will be <10%, >70% of participants will be satisfied, and we will assess mothers’ feedback on the intervention. Feasibility analysis will be conducted once 45 participants reach 6 months post partum.

Methods: We will aim to recruit 45 participants given a 30% attrition rate in this feasibility randomized trial. Eligible mothers are more than 18 years old, have a diagnosis of HDP (seated BP >140 mmHg systolic or >90 mmHg diastolic or UPCR >0.28g/g), have a singleton pregnancy delivered at >34 weeks gestation, and intend to breastfeed with breastfeeding initiated before hospital discharge. Mothers receive phone calls from the research nurse every week for the first 6 weeks after delivery, as well as an in-person booster session at 3 months postpartum, with possibility of reaching out to the research nurse anytime during 6 months after having given birth.

Anticipated Results: We anticipate that the self-efficacy based breastfeeding intervention will lower blood pressure in women who have had HDP. As for its feasibility in this specific population, we hope to gather information on challenges, barriers, and facilitators of breastfeeding as well as on preferred methods of intervention to adapt and offer a better-tailored intervention for a subsequent multi-centre trial.
Phenotypic and Functional Characterization of Four IPEX Mutations in the human FOXP3 gene.

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Introduction: IPEX syndrome (immune dysregulation polyendocrinopathie enteropathy X-linked) is a rare disorder of immune regulation which causes an aggressive autoimmune and inflammatory syndrome, leading to premature death in the first year of life. The clinical presentation is classically the triad autoimmune enteropathy, autoimmune endocrinopathy (type 1 diabetes) and autoimmune eczema dermatitis. There is currently no consensus on IPEX treatment; the only truly effective treatment to date remains hematopoietic stem cell transplantation. This syndrome results from germline mutations in the FOXP3 gene encoding a DNA forkhead binding domain transcription factor driving regulatory T (Treg) cell development. The induction and maintenance of FOXP3 expression is essential for the development and function of Treg cell lineage. Over 60 different FOXP3 mutants have been discovered, although the impact of each mutation on FOXP3 expression and Treg cell function remains poorly defined. Four functional domains characterize the structure of FOXP3, however over 90% of the IPEX mutations take place in the DNA binding forkhead domain. Here, we aim to characterize the ability of different IPEX mutations to impact the Treg cell phenotype.

Material and Methods: We used a plasmid transfection technique in HEK 293 Tx cells to generate lentivirus in order to stably transduce primary, human CD4+ T cells with different FOXP3 mutants. Following in vitro expansion for 10 days, transduced T cells were sorted and activated, and assessed for their expression of Treg cell markers (FOXP3+, CD25high, CD127low) and production of cytokines.

Results: Transducing cells with FOXP3WT induced a Treg cell phenotype defined as FOXP3+ CD25high CD127low. The FOXP3C424Y mutation was the only IPEX mutation which retained this phenotype. CD4+ T cells transduced with FOXP3R347H, FOXP3R397W or FOXP3I363V mutants did not force a Treg cell surface phenotype. FOXP3R347H and FOXP3I363V T cell transductants developed an intermediate Treg cell phenotype, as determined by levels of CD25, CD127 and FOXP3 expression. Consistently, FOXP3C424Y and FOXP3R347H repressed the production of the proinflammatory cytokine IFNγ, in T cells, consistent with the transcriptional repressive functions of FOXP3 on inflammatory genes. In contrast, FOXP3R397W failed to repress the production of IFNγ.

Conclusion: The study of IPEX mutations represents an important strategy for the molecular dissection of FOXP3 functions in Treg cells. Future work will be aimed at identifying transcriptional differences among mutants, assessing the capacity for protein-protein interactions with the different FOXP3 mutations, and evaluating Treg cell suppressive function.
Biodegradable nanomaterials for implantable glucose oxygen biofuel cells

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With the emergence of transient electronic implants to measure and monitor physiological markers, there is a urgent need to engineer biodegradable implantable energy source. Among them, the biofuel cell can generate electrical energy directly from glucose and oxygen with electrocatalysts. Here we develop an electrocatalyst combining two bioresorbable materials, 2D layer iron oxide with ZnO nanoflowersto reduce oxygen.
Characterizing the Effects of Chlorine-induced Airway Injury on Endoplasmic Reticulum Stress in a Murine Model

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Background: Airway exposure to Cl₂ causes oxidative damage to the airways, associated with acute inflammation and airway hyperresponsiveness (AHR). Numerous studies have linked oxidative damage to endoplasmic reticulum (ER) stress. However, the direct effects of Cl₂ exposure on ER stress in the lungs have not been well studied. ER stress occurs when an overabundance of unfolded proteins is present in cells. To return to proteostasis, the Unfolded Protein Response (UPR) is activated, resulting in decreased protein translation, increased degradation of unfolded proteins, and increased expression of chaperones. The objective of our study was to characterize the effects of Cl₂ exposure on ER stress in the lungs.

Hypothesis: We hypothesized that Cl₂ induces airway injury, which is associated with the induction of the ER stress markers, GRP78 and CHOP.

Methods: BALB/c mice were weighed before and after nose-exposure to either Cl₂ gas (1xCl₂ group) at 100ppm for 5 minutes or air. Mice were sacrificed 24 hours later. AHR was assessed with a Flexi-vent™; inflammation was quantified from the bronchoalveolar lavage (BAL) fluid; GRP78 and CHOP were assessed in the lungs via Western blot and flow cytometry. GRP78 and CHOP were also evaluated by immunofluorescence in naïve alveolar macrophages stimulated in vitro for 1 hour with hypochlorite, an aqueous Cl₂ oxyanion.

Results: Compared to the air-exposed mice, the 1xCl₂ group lost weight and their BAL showed increases in total cells, macrophages, and neutrophils. AHR in these mice were similarly enhanced following Cl₂ exposure. Furthermore, the assessment of GRP78 and CHOP through Western blots showed an increase in only GRP78 in the lungs of 1xCl₂-exposed mice. Preliminary flow cytometry results indicated that CHOP may be enhanced in the 1xCl₂ group. Moreover, in vitro stimulation of the naïve alveolar macrophages with hypochlorite showed an increase in GRP78 and CHOP.

Conclusions: Chlorine-induced airway injury, characterized by inflammation and AHR, causes increases in ER stress markers, GRP78 and CHOP.
Cystinosis is an autosomal recessive disease caused by mutations in the CTNS gene, which encodes a cystine-selective efflux channel in the lysosomal membrane. Loss of CTNS protein causes intralysosomal cystine accumulation and deterioration of the kidneys, thyroid, pancreas, retina and other organs. Current therapy with oral cysteamine chemically mobilizes lysosomal cystine and slows organ deterioration but is not a cure. A likely explanation is that the CTNS protein may be important for other cellular functions, including autophagy. At the autophagolysosomal step, there is degradation of p62 protein, a marker for autophagy. CTNS mutant cells exhibit a defect in p62 processing. About 15% of Cystinosis patients harbor CTNS nonsense mutations that block mRNA translation. These patients might benefit from new nontoxic aminoglycosides such as ELX-02, which bind to the mammalian ribosome and induce translational readthrough of nonsense mutations. We used FACS to isolate HPV-immortalized proximal tubular cells from the urine of healthy controls and from a patient with the CTNS W138X nonsense mutation in compound heterozygosity with a CTNS deletion. Control and mutant cells were grown in monolayer and exposed to cysteamine or to ELX-02 for 72 hours. We evaluated p62 level by ELISA and Western blot. We observed that CTNS\textsuperscript{W138X/57kd} cells had a higher level of p62 than controls. After exposure to either ELX-02 or cysteamine, p62 concentration in mutant cells decreased. CTNS\textsuperscript{W138X/57kd} mutant cells accumulate p62; we speculate that this reflects defective processing of autophagolysosomes. Pathologic accumulation of p62 can be largely reversed by exposure to either ELX-02 or cysteamine.
Functional assay of CD8 T-cells in bronchoalveolar lavage fluid and peripheral blood in persons living with HIV on suppressive antiretroviral therapy

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Cytotoxic CD8 T lymphocytes, play a key role in anti-HIV specific immune responses by t via their diversified arsenal including cytokines (eg. IFN-γ, TNF-α, IL-2), granules containing perforin and granzymes, and the Fas ligand. These allow CD8 T-cells to kill infected target cells, activate macrophages, and mediate pro-inflammatory processes.

These effector functions may be impaired in the lungs of persons living with HIV (PLWH), rendering them susceptible to opportunistic respiratory infections. Even after the administration of antiretroviral treatment (ART), HIV-infected persons are 25 times more likely to suffer from pneumonia than HIV-uninfected individuals. Furthermore, CD8 lymphocytic alveolitis is common among HIV positive patients, even if they show no symptoms of a lung infection. Some of the effector functions of CD8 T-cells in the peripheral blood could be recovered after ART initiation, however, this is not the case for the CD8 T-cells in the lung. Importantly, CD8 T-cell dysfunction is linked to HIV persistence.

Our lab has previously documented that HIV persists within the lung mucosa of long-term ART treated patients with undetectable plasma viral load. The amount of total HIV DNA in BAL cells was significantly higher than in peripheral blood mononuclear cells (PBMCs). We therefore hypothesize that HIV persistence in the lungs likely leads to long term CD8 T-cell activation, which can exhaust these cells and compromise their cytotoxic activity. Using BAL fluid from HIV+ (with suppressed viral load for at least 3 years on HAART) and HIV- donors (both tobacco smokers and non-smokers) we are optimizing in vitro functional assays to assess HIV-specific poly-functionality of pulmonary CD8 T-cells as well as their immune activation/exhaustion/senescence profile compared to CD8 T-cells from the blood. CD8 T-cells will be FACS-sorted and phenotypically characterized using flow cytometry. We will also analyze their cytokine expression after HIV antigen stimulation, and optimize the protocol for a killing assay that will later be used to evaluate their cytotoxicity.
Murine Bladder Cancer Organoids

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**Background:** Bladder cancer is one of the most prevalent cancers in North America, yet treatment options are limited and have not improved for decades, despite high incidence rates. One main obstacle to this is the relative lack of model systems that faithfully recapitulate the biology of bladder cancer. Traditional 2D cell culture models do not accurately reflect the biology of the disease, dampening the development of novel therapeutics. In vitro 3-dimensional (3D) methods offer an alternative to the traditionally-used 2D cell cultures. Organoids, 3D cultures of bladder (cancer) cells, encapsulate many of the structural and functional aspects of in vivo counterparts, including gene expression and tumour development. A protocol has been reported for organoid culture of human and mouse bladder cancer tissues, however murine bladder cancer cell line organoids have yet to be established.

**Methods:** MB49 mouse bladder carcinoma cells were injected sub-cutaneously in mice, to model tumour development. When the tumour was palpable (approximately 2 weeks), tumour cells were excised and collected in Advanced DMEM/F12 media supplemented with ROCK inhibitor, Primocin, and Glutamax. The tissue was digested using liberase and suspended in Matrigel, then seeded in 4 wells of a 24-well plate at 4 concentrations (50,000; 100,000; 250,000; and 500,000). The organoid cells were cultured in organoid growth media: Adv. DMEM/F12 supplemented with FGF10, FGF7, A83-01, B27, and Pen/Strep. The organoid growth media was changed every 2-3 days, and the organoids were passaged every 7 days.

**Results:** After approximately 2 weeks, the sub-cutaneous tumour was palpable, and sufficient for tissue excision. The resulting murine bladder organoids showed positive growth after only 3 days in media, and continued propagation over time with media change and passaging. After 3 days, the cells began aggregating into small structures visible under the microscope. After 7 days, the cell aggregates had developed into more complex 3D structures. After the first passage on day 7, the organoid cells retained their 3D aggregated structure.

**Conclusion:** This study affirms that organoids can be grown from in vivo cancer cells, presenting researchers with an ideal model to investigate disease markers and treatment response in bladder cancer. We are currently further investigating mouse-derived organoids from an orthotopic model. In addition to this, we are also investigating murine-derived organoid transplantation, by re-injecting organoid cells into mice. This could offer a more comprehensive model for investigating treatment response and disease progression.
The effects of 17ß-estradiol & progesterone treatments on ligament regeneration

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Anterior cruciate ligament (ACL) injuries are highly common injuries of the knee. The ACL has large avascular zones which is challenging for tissue regeneration. Surgical reconstruction is the current gold standard for ACL injuries in active patients which restores gross joint stability. Despite this, post-traumatic osteoarthritis and other complications are common. Interestingly, females seem to be more susceptible to ligament injury than males participating in similar athletic activities. The cause of this sex discrepancy can be multifactorial, however an important aspect shown in several reports indicates that hormones such as progesterone and 17ß-estradiol play a role. In this study, ligament cells were isolated from two female and two male donors, pellets cultures were generated and treated with varying concentrations of these hormones. After 21 days of culture, microscopic images were captured for surface area analysis. To measure metabolic activity, AlamarBlue assay was performed on each donor, under each condition. Additionally, histological assessment of collagen type I and proteoglycan was performed using immunostaining and Safranin-O/fast green. Western blot analysis and qPCR was performed to determine ligament associated protein and gene expression. The results for male and female donors will be compared to determine the effects of these hormones on tissue laxity. Our data may provide evidence for potential hormone treatments (i.e. varying forms of contraception) to increase ligament strength and decrease risk of ACL injuries in females.
Restricted Mean Survival Time of Older Adults Referred For But Not Undergoing Transcatheter Aortic Valve Replacement

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Introduction: A subpopulation of older patients with symptomatic aortic stenosis are referred for transcatheter aortic valve replacement (TAVR) but do not undergo any procedure. We sought to categorize the clinical and geriatric profiles of patients not undergoing TAVR and determine their restricted mean survival time (RMST).

Methods: Older adults assessed between 2014-2018 at the McGill TAVR clinic were prospectively enrolled. In addition to patients who underwent TAVR (Group A), those who did not undergo a procedure within one year of their clinic evaluation were categorized according to the following reasons: patient (Group B) or physician (Group C) decision not to proceed, waiting for the procedure or for a decision to be made (Group D), undergoing valvuloplasty as a potential intermediate to TAVR (Group E). For patients in each group, the RMST and Cox proportional hazard ratio for mortality were computed over 1 year adjusting for the Society of Thoracic Surgeons risk and Essential Frailty Toolset score. Patient-level predictors for not undergoing TAVR were examined using multivariable logistic regression.

Results: The cohort consisted of 377 patients with a mean age of 82.3 years, of which 233 underwent TAVR and 144 did not. Relative to group A (N=233), the difference in the adjusted RMST was -29 days (95% CI -67, 8) in group B (N=24), -36 days (95% CI -63, -10) in group C (N=68), -141 days (95% CI -203, -78) in group D (N=29), and 5 days (95% CI -29, 38) in group E (N=23). This corresponded to an adjusted hazard ratio for mortality of 3.64 in group B (95% CI 1.50, 8.84), 3.75 in group C (95% CI 1.93, 7.23), 14.00 in group D (95% CI 6.70, 29.25), and 1.33 in group E (95% CI 0.45, 3.93). Kaplan-Meier survival curves were superimposed for TAVR and valvuloplasty patients until 8 months, after which valvuloplasty patients accrued more fatalities. Patient-level predictors for not undergoing TAVR were: age ≥90 years, high Essential Frailty Toolset score, disability for activities of daily living, severe lung disease, severe kidney disease, and reduced left ventricular ejection fraction.

Conclusion: Older patients who are referred for TAVR but do not undergo a procedure have reduced survival time, especially when waiting for the TAVR procedure or decision. Those undergoing a valvuloplasty appear to be protected for approximately 8 months. Efforts should be made to minimize TAVR wait times or consider balloon valvuloplasty when a TAVR decision is deferred.
Transcranial Magnetic Stimulation In The Primary Visual Cortex

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Transcranial Magnetic Stimulation (TMS) is a brain stimulation technique using magnetic fields to induce electrical current in the brain, and is used treat a wide variety of mental and neurological conditions. This stimulation can cause motor activity when the motor cortex is stimulated, or the perception of blob like image called a phosphene when the primary visual cortex is stimulated. Just how that current causes these behavioural changes is a matter of open research and depends on the frequency and location of stimulation.

This experiment aims to investigate some of these unknowns. We applied repetitive TMS treatment for 40 seconds to the primary visual cortex (V1) in order to measure the effect of this stimulation on psychophysics visual discrimination thresholds. Thresholds were tested under visual mask conditions in order to look at surround suppression and cross-orientation suppression. These stimuli were chosen to tease out the suppression effects of TMS.

Subjects drew phosphenes on a monitor display in order to report their percept. Phosphene locations in the subject’s visual field correspond to the retinotopic location in V1 that is stimulated. This allowed us to match up the retinotopic location of the psychophysical stimuli and the area of brain stimulation. Another interesting side effect of our phosphene drawing procedure was the characterization of the wide range of possible phosphenes seen by subjects. We hypothesis that this variability might correspond to the wide variability of psychophysical data collected.

Individual brains respond differently to TMS, and these differences are important to understand in the context of basic research and potential therapeutic applications.
Parathyroid Cell Transcription Factor Glial Cells Missing-2: Novel Inactivating and Activating Mutations Associated with Hypoparathyroidism and Hyperparathyroidism, Respectively

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Context: Glial cells missing -2 (GCM2) is a transcription factor expressed in the parathyroid hormone (PTH)-secreting cells of the parathyroid glands and is essential for their development in terrestrial vertebrates. Primary hypoparathyroidism encompasses a heterogeneous group of conditions in which hypocalcemia and hyperphosphatemia occur as a result of deficient PTH secretion. Inactivating mutations in the parathyroid cell-specific transcription factor GCM2 cause familial isolated hypoparathyroidism (FIHP) inherited in either a recessive or autosomal dominant fashion. FIHP has been defined as hereditary primary hyperparathyroidism without the association of other disease or tumors. Activating mutations in GCM2 predispose to FIHP.

Objective and Subjects: To identify the causative mutations in two families with affected individuals presenting with hypoparathyroidism and twenty-four families presenting with hyperparathyroidism.

Methods: We used leukocyte DNA of hypoparathyroid individuals to assess CASR, PTH, GNA11 and GCM2 gene mutations and that of hyperparathyroid individuals to assess MEN1, CDC73, CASR and GCM2 gene mutations. GCM2 variants that we identified were evaluated by in vitro functional analysis in a transcriptional luciferase reporter assay containing a GCM2 binding site.

Results: A homozygous novel c.199C>T; p. R67C GCM2 variant was identified in affected members of both hypoparathyroid families. In Western blot analysis, the R67C mutant demonstrated equal protein expression relative to wild-type (WT) GCM2, but only basal transcriptional activity in the in vitro luciferase reporter assay, in which WT GCM2 was 13-fold more active than basal. Structural modeling indicated that the mutant C67 variant had lost the ability of WT R67 to interact with DNA. Heterozygous GCM2 variants were identified in affected individuals of four of the hyperparathyroid families. These variants lie within a C-terminal conserved inhibitory domain, including: c.1144G>A;p.V382M (previously described); c.1149C>G;p.I383M (novel); c.1156A>T;p.T386S (novel); and c.1181A>C;p.Y394S (previously described). Although protein expression of these mutants, was at the same level as WT GCM2, each demonstrated significantly greater in vitro functional activity than WT.

Conclusion: We have identified a novel inactivating mutation in the GCM2 gene and provide evidence that it is implicated in hypoparathyroidism. We have also identified novel activating mutations of the GCM2 gene and provide evidence that they contribute to hyperparathyroidism.
Poster Presentations — Abstracts
A-1 The role of folate insufficiency and excess during kidney and urinary tract development

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Background: Vitamin B9, or folate, is the one-carbon source for critical cellular pathways involved in DNA and RNA synthesis and methylation. Embryonic kidney development is affected by maternal environmental factors like diet that can induce changes in DNA methylation resulting in gene activation or repression. Evidence suggests that both low and high maternal folate intake can be deleterious for embryonic kidney and urinary tract development. Defects in kidney development can be severe like the absence of kidney formation or mild like a decrease in the number of nephrons that form. Defects in urinary tract development can manifest as vesico-ureteric reflux (VUR) in which urine refluxes from the bladder to the kidneys or in obstruction. Along with the liver and intestine, the kidneys play a key role in folate metabolism. In the liver, a high folate intake results in down-regulation of Methylenetetrahydrofolate reductase (MTHFR), which is a key enzyme in DNA methylation and folate metabolism, however this has not been studied in the kidney.

We hypothesize that offspring exposed to insufficient or excessive folate doses will exhibit a defect in kidney formation, a decrease in nephron number, or urinary tract defect.

Methods: To test this hypothesis, CD1 female mice were maintained on a high folate (5-fold higher, n=11), a low folate (5-fold lower, n=11) or a control diet (2mg/kg folate, the recommended dietary allowance, n=11) for 3 weeks and then bred to CD1 males. The offspring from these crosses will be dissected at 4 time points: embryonic day (E) 15 (when the urinary tract connects to the bladder), E17.5, postnatal day (P)1 and P10 (when nephron formation is complete). Pups will be tested for VUR. The kidneys and bladder of the offspring will be processed for histological analysis. The number of nephrons will be counted in right kidneys and MTHFR protein levels will be assessed in left kidneys from pups exposed to each diet using western-blot.

Results: None of the newborn mice on a high folate diet exhibited VUR (0/15). Newborn mice exposed to control and deficient diets will be tested for VUR. The E17.5 embryos exposed to a high folate diet exhibited larger right kidneys (n=7, p<0,05) compared to embryos on the control diet (n=6). The other experiments described above are in progress.

Conclusion: Preliminary results suggest that high folate intake is not a risk factor for vesico-ureteric reflux, but it does lead to larger kidney weights in the embryo.
A-2 Highly porous elastomer scaffolds for the ligament and cartilage tissue engineering

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Background & purpose: Ligament and cartilage damage often occurs as a result of sports-related injuries. Poor alignment of the joint, excessive weight/activity, overuse or injury can cause further damage to these tissues. As avascular tissues, self-repair of these cells is intrinsically limited, so intervention is required to recover tissue structure. With proper scaffold design, the viscoelastic nature of these tissues may be replicated with LAYFOMM; a thermoplastic polyurethane (TPU) co-polymer with polyvinyl alcohol (PVA). These scaffolds are produced using 3D printing. They are nanoporous and incorporate macro-pores that allow for deposition of ligament and chondrocyte cells and the formation of collagen-rich matrices. By supplementing these scaffolds with specialized media, their ability to promote deposition and regeneration of collagen-based matrices can be investigated.

Methods: Using fused-deposition modeling, these scaffolds are produced. All scaffolds were printed using a Flashforge Creator Pro, with a 0.3mm nozzle at a print temperature of 220°C, 50°C bed temperature, at 18mm.s⁻¹. After printing, they were washed with distilled water to remove excess PVA, leaving a highly porous structure. Ligament and chondrocyte cells were held in culture for 21 days (high glucose DMEM, supplemented with 10% FBS, and 1% penicillin streptomycin), whilst changing media every 2-3 days. Following culture, the cells were counted, and seeded in the scaffolds in a 24-well plate, with 400,000 cells on each scaffold. Samples for each cell type were supplemented with: 1) 10% FBS media, 2) chondrogenic control media (serum-free), 3) chondrogenic media (serum-free, with TGF-β1). Following 21 days of culture, cell proliferation, viability, western blot, and qPCR were performed.

Results: The addition of serum (10% FBS) showed increased proliferation of these cells. Deposition of extracellular matrix was visible in the pores of these scaffolds. Preliminary results show the expression of genes specific to chondrocytes and ligament-derived fibrocytes. Specifically, using qPCR, it was shown that cells from ligaments expressed higher levels of scleraxis and collagen type VI. Live/dead assay demonstrated the viability of ligament and chondrocyte cells, and those embedded in the collagen-meshes. The proteins of interest for chondrocyte tissue are collagen II and aggrecan, while that of ligament tissue is collagen I.

Conclusions: The use of LAYFOMM scaffolds can lead to the deposition of collagen-rich matrices. The production of ligament and chondrocyte extracellular matrix is anticipated, which may in-turn provide a novel treatment for tissue damage caused by sports-related injuries.
A-3 Patient-Powered Research Using the Multi-Institutional Opal Patient Portal

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Introduction: Opal is a smartphone app that allows patients to view their medical data and enables clinicians to send them personalized educational material and patient-reported outcome questionnaires (opalmedapps.com). Currently, Opal is in use at the Cedars Cancer Centre of the McGill University Health Centre (MUHC). Our objectives are to expand Opal to multiple hospitals simultaneously—allowing patients to access all of their medical data via one login—and to use this connected infrastructure to allow patients to donate their data from all of their institutions to a secure central research database. Six cancer centres in the Montreal area (St. Mary's Hospital Center, CHU Sainte-Justine, CHUM, Hôpital Maisonneuve-Rosemont, Hôpital de la Cité-de-la-Santé de Laval, and the MUHC) are participating in the project, with funding from the Canadian Partnership Against Cancer.

Methods: The existing Opal platform was studied to determine the necessary changes for a multi-institutional implementation and for data donation. The data storage, the app's data request process, and the user registration system were revised after comparing the pros and cons of various design options.

Results: A model for a multi-institutional Opal was designed, a prototype was implemented and the platform was presented to the MUHC Security and Governance team. The new data storage and retrieval system involves replicating the existing Opal database and backend software identically in each connected hospital, with an additional shared database and software for central storage of common data, including a research database for the storage of donated data. Customization was added to grant or deny access for each hospital to different features in the app. Additionally, a mockup was developed to demonstrate how data can be displayed to the patient together with identifying information indicating the source hospital for each data element.

Discussion: Opal's new design reuses much of the existing single institution infrastructure, but involves modifications at each level (databases, backend software, registration system, frontend application). The development of a prototype implementing the new design is complete. This proof-of-concept prototype will be developed into a production version which will be deployed in August 2019 at St. Mary's Hospital Center and Cité-de-la-Santé de Laval.
A-4  Calculating the G-value for hydrated electrons using Geant4-based simulation

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Background: Radiolysis of water is the decomposition of water molecules by ionizing radiation, where hydrated electrons are amongst the numerous short-lived radicals produced. By monitoring the concentration of hydrated electrons using absorption photometry, the absorbed radiation dose to water can be measured—a technique called hydrated electron dosimetry. A solution of water-based dosimeter prototype (0.01 M NaOH) encased in a glass cavity was irradiated with varying energies of photon beams from a Varian TrueBeam medical linear accelerator for ionization. A laser beam is then passed through the solution; it is reflected back and forth between four dielectric mirrors, yielding an optical path length of 40 cm, and its intensity was recorded at readout. Using this measured intensity along with other parameters such as the physical density of the solution, the absorbed radiation dose (Gy) can be computed. One of the various variables in the equation relating the radiation absorbed dose to the laser’s intensity is the radiation chemical yield (G-value). The G-value is reported to be (3.0 ± 0.3) per 100 eV in pure water. It has, however, a large uncertainty, since the 2-mm thick glass cavity as well as the 1% NaOH in water solution need to be taken into account.

Aim: The aim of this study is to through Monte Carlo simulations calculate the G-value in order to obtain a more accurate value for our cavity and radiation quality.

Method: A Geant4-based simulation package was developed to calculate the G-value for hydrated electrons. 1% NaOH in a 60-mL water solution encased in a 2-mm thick silica glass cavity was modelled in the software package. Incoming particles from the linear accelerator are read from IAEA-formatted phase space files. The phase space file describes the position, momentum, and energy of the photons leaving the linear accelerator.

Results & Conclusion: The geometry and beam was accurately modelled in the software package. The goal for the end of the summer is to successfully simulate the G-value with this software in order to more accurately compute the absorbed radiation dose. Once the G-value can be reliably calculated with different photon beam energies and different world volumes according to our experiment’s parameter changes, the uncertainties in our results will be reduced.
A-5 The impact of estrogen on cytokine synthesis by bronchial airway epithelial cells infected with Pseudomonas aeruginosa

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Life expectancy of people living with cystic fibrosis (CF) has greatly increased in the last few decades, however, the greatest number of deaths occur in the 21-30 years old age group. A major predictor of disease progression in CF patients is the frequency of pulmonary exacerbations (PEx). Data collected from a cohort of CF patients from the Montreal Chest Hospital suggests that frequent PEx are more common in female patients and are linked to chronic mucoid Pseudomonas aeruginosa infection. To understand this correlation, the impact of estrogen on the response of bronchial airway epithelial cells to infection by P. aeruginosa was studied by looking at the expression of inflammatory cytokines.

We hypothesize that estrogen decreases the synthesis of cytokines, of the IL-1 family, in bronchial epithelial cells infected by P. aeruginosa, making them more susceptible to viral infection, a known driver of PEx.

To investigate the response of the bronchial epithelial cells to estrogen, immortalized human bronchial epithelium cells (BEAS-2B) were treated with a range of concentrations of 17b-estradiol or PAOI filtrates. This model allowed the induction of the signaling pathways to be analyzed by observing the phosphorylation of p38 and ERK MAPK by western blot. The mRNA expression of the IL-8 and IL-6 genes were analyzed by qPCR and the protein production of IL-8 was analyzed by ELISA. To investigate the combined effect of estradiol and the filtrates, a co-stimulation was performed. Cells pre-treated with estradiol were stimulated with filtrates as a model of infection in cells chronically exposed to estrogen. Some studies showed that P. aeruginosa is able to invade and persist in airway epithelial cells, hence we decided to investigate the effect of 17b-estradiol pre-treatment on the intra-cellular survival of P. aeruginosa.

The preliminary results of the experiments detailed above, suggest that treatment with 17b-estradiol increases IL-8 mRNA production and IL-8 secretion in BEAS-2B.

The induction of IL-8 suggests that estrogen may increase the synthesis of IL-8 in bronchial epithelial cells infected by P. aeruginosa. Further investigations are needed to determine if estrogen increases other cytokines, such as the ones of the IL-1 family and how this increase modulates the inflammatory response triggered by P. aeruginosa infection. The purpose of this investigation is to better understand the mechanism underlying sex differences in CF patients, and how these differences may impact the interaction between bacterial and viral infections in CF patients.
A-6  Opal, the Patient Portal: Pilot Release and Beyond

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Introduction: With the goal of increasing patient involvement in their healthcare, a patient portal called Opal (opalmedapps.com) was created. For the past year at the Cedars Cancer Centre (CCC) of the MUHC, Opal has been in pilot release, with over 250 registered patients. To do so, patients must present themselves at the CCC Foundation kiosk, where an employee will register them. The current registration process is not ideal. As such, a new registration process is being developed, allowing patients to create their accounts from home. The workflow of the registration process has been documented, with a view to improvement, prior to expansion to other hospitals. The Montreal Children’s Hospital (MCH) has expressed their interest in making Opal available to their patients. To start, Opal will be rolled out to parents and patients in the MCH-Nephrology department.

Objective: The goal of this project was to improve the current registration workflow of the pilot release at the CCC and use knowledge thus acquired to improve the workflow prior to expansion to MCH-Nephrology.

Methods: To determine the amount of time spent by an employee to register patients for Opal, timestamps for the start and end of the process were recorded for each patient. For the expansion project, a questionnaire was distributed in the waiting room to parents and patients (user-patients) in the MCH to assess their preferred levels of access to their personal health information (PHI) using a mobile phone app.

Results: The registration of 100 patients was documented, where the registration process takes an average of 18.5 minutes to complete. Employees dedicated a total of 27 hours over 6 weeks to patient registration. For the questionnaire, we obtained 100 responses from seven clinics in the MCH. It was found that 68% of user-patients would prefer to receive their PHI as soon as it is available, 22% would prefer only receiving their PHI after speaking with their doctor, and 10% wanted to only view basic information (their appointment schedule and educational material).

Discussion: Upon the release of the new patient registration module, hospital employees will only be required to generate a code that patients will use to register themselves online, thus reducing the time spent by employees on Opal related tasks. Finally, the finding that 68% of questionnaire respondents want to view all their PHI via a mobile phone app is useful information for planning the upcoming expansion to the MCH-Nephrology department.
A-7  Longitudinal Natural History Study of Peroxisome Biogenesis Disorders in the Zellweger Spectrum: Management Guidelines for Adolescent and Adult Patients

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Background: Peroxisome Biogenesis Disorders in the Zellweger Spectrum (PBD-ZSD) are a heterogeneous range of disorders caused by a compromised ability to assemble functional peroxisomes inside cells, resulting in consequences on multiple organ systems. PBD-ZSD has an estimated incidence of 1/50,000 and is caused by biallelic mutations in any of the 13 PEX genes required for peroxisome assembly. Although the disease spectrum is broad, most patients have an intermediate to mild form and many survive into adulthood. In addition, new diagnoses are being made in adolescents and adults. There are currently no curative therapies for this disorder, but supportive care is available to manage disease symptoms. We and others published reviews of clinical manifestations and treatment guidelines for all patients, though geared towards children. PBD-ZSD adolescents and adults manifest a different disease progression when compared with children, and thus face their own unique challenges. Therefore, generating adult-specific guidelines is crucial for healthcare professionals and caretakers to ensure optimal care for these PBD-ZSD patients.

Hypothesis: Clinical data extracted from medical records of PBD-ZSD individuals aged 13 and older, video calls with these families, and discussion groups held at the Global Foundation for Peroxisomal Disorders' 2019 conference will provide a better understanding of the course of all disease symptoms, standards of care, and challenges in pediatric-to-adult care transitions. The adult-specific care management guidelines generated will benefit these patients as well as the entire peroxisomal disease community. A better description of the natural history of the disease in adults will enable identification of reliable clinical endpoints for future interventional trials.

Methods: We will review medical records of the 48 PBD-ZSD adolescents and adults enrolled in our REB-approved Longitudinal Natural History Study on Peroxisomal Disorders. We will enter clinical descriptions and test results of a system review through our custom-made Access database. Simultaneously, we will organize video calls with the patients and families to collect information about their medical issues, main challenges, the pediatric-to-adult transition experiences, and any information they consider critical to include in an adult-specific guidelines publication. With this information collected, we will establish the questions to address for this project and extract the relevant data from our database.

Expected outcomes: We will analyze this data and report our findings as a care management guideline resource for adolescents and adults with PBD-ZSD. The data collected will be kept in our database to be used for future studies within our Natural History Study project.
A-8  Parkin Overexpression Attenuates Muscle Atrophy and Rescues Mitochondrial Morphology in Sepsis-Induced Skeletal Muscle Dysfunction

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Rationale: The accumulation of mitochondrial dysfunction is believed to contribute to skeletal muscle weakness and loss in severe sepsis. Changes in mitochondrial mitophagy, dynamics and morphology can greatly impact mitochondrial function, and vice versa. However, whether mitochondrial mitophagy, dynamics and morphology in skeletal muscle are altered in sepsis remain largely unexplored. Here, we aimed to (1) investigate the effects of sepsis on mitochondrial dynamics and morphology in skeletal muscle; and (2) evaluate the impact of parkin overexpression, a protein in charge of the removal of dysfunctional mitochondria, on muscle fiber size and mitochondrial morphology using a quantitative 2-dimensional transmission electron microscopy approach.

Methods: Parkin was overexpressed for 4 weeks in the gastrocnemius (GAS) muscles of 4 week-old mice using intramuscular injections of Adeno-Associated Viruses (AAV). A control AAV, containing a sequence coding for the green fluorescent protein (GFP), was injected in the contralateral leg. Sepsis was induced by cecal ligation and perforation (CLP). Control (Sham) mice were subjected to the same surgery, but the cecum was neither ligated nor punctured. The impact of sepsis and Parkin overexpression on muscle myofiber size, mitochondrial morphology and gene expression were investigated.

Results: As expected, CLP resulted in a significant decrease in body weight 48 hours after surgery. Sepsis increased the expression of MuRF1 and Atrogin-1, suggesting increased protein degradation. In line with these findings, CLP mice displayed an increased abundance of small fibers, a clear sign of atrophy. Parkin overexpression attenuated myofiber atrophy in CLP mice and resulted in myofiber hypertrophy in Sham mice. Septic muscle displayed enlarged and more complex Intermyofibrillar (IMF) mitochondria. Interestingly, Parkin overexpression reduced the morphological complexity of IMF mitochondria in both Sham and CLP mice. Sepsis decreased the expression of TFAM, complex II and complex IV, while Parkin-overexpressing muscles were protected. Sepsis increased the expression and content of LC3-II, SQSTM1 and BNIP3. Parkin overexpression did not affect the expression and content of these proteins.

Conclusions: The present study shows that sepsis alters mitochondrial morphology in skeletal muscles, an effect attenuated by Parkin overexpression. Our results also indicate that Parkin overexpression attenuates sepsis-induced myofiber atrophy. Although further studies are required, our findings place Parkin as a potential therapeutic target to counter sepsis-induced muscle dysfunction. Keywords: Sepsis; Mitophagy, Muscle Atrophy; Mitochondria, Autophagy
Models to engage children as patient-partners: A scoping review

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Purpose: The purpose of the present scoping review is to comprehensively review the literature to explore which models have been used to engage children as patient-partners in healthcare. Sub-objectives are to explore how these models were used and document ethical challenges that were raised and how they were addressed.

Methods: Arksey & O’Malley’s revised scoping review framework will be used to guide the article identification and analysis. Searches were performed in key health-related databases using different combinations of the specific search terms identified in collaboration with the librarian. The inclusion criteria for this scoping review will be any study published between 1980 and 2019 and related to children as patient-partners.

Preliminary findings: Preliminary findings suggest that focusing on parents’ beliefs of treatments, rather than children’s, builds an asymmetric relationship towards the child. Therefore, some framework suggests moving from a family-centred to a child-centred care approach, by recognizing children as active agents in their own care. Children should be actively involved in the planning of their care and included as patient-partners to participate in decision-making. According to another model, three main actors are involved in child healthcare: the healthcare professional, the parent and the child. They propose that a partnership should be built between the professional and the child, rather than between the professional and the parent. Children could thus benefit from these models to meet their individual needs, goals, and priorities.

Conclusions: In order to improve patient-partnership with children, this scoping review is needed to identify and synthesize the literature on children as partners in healthcare. This review is also expected to provide insight into how to ethically engage children. Involving patients as partners in healthcare raises ethical challenges – such as managing power differentials. However, partnering with children remains a challenge, despite its potential to render more child-centered services that would fulfill children’s needs.

Clinical relevance: Recently, the notion of patient engagement in research and health services planning has become best practice. Partnering with patients has been shown to improve the outcomes, as well as quality of life. The literature available on children as patient-partners, the focus is older youth or parents’ beliefs. For children to be included, adequate safeguards need to be in place, which this study will seek to identify. The knowledge of this project will be of relevance to researchers, clinicians and managers who aim to engage children as patient-partners.
The adapter protein Dok-4 binds to Rho GTPase-activating proteins (GAPs) in a tyrosine kinase-regulated manner through its PTB domain

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The Dok family of adapter proteins is composed of seven members structurally characterized by an N-terminal tandem of homologous pleckstrin homology (PH) and phosphotyrosine-binding (PTB) domains, thought to promote interaction with membrane phospholipids and tyrosine phosphorylated protein partners, respectively. Dok-4 is expressed predominantly in epithelial tissues and cells, where it exerts inhibitory actions downstream of receptor and non-receptor tyrosine kinases. However, the identity of effector molecules implicated in Dok-4 action remain largely unknown. Rho GTPases are molecular switches which control the actin cytoskeleton of podocytes, specialized kidney epithelial cells that form an important part of the glomerular filtration barrier. Mutations in elements of the signalling pathway towards controlling these GTPases causes aberrant podocyte health and thus leads to a host of proteinuric nephrotic diseases. We have recently found that Dok-4 interacts with β2-chimerin (Chn2), a GTPase-activating protein (GAP) for the Rho family GTPase Rac1, and facilitates its inhibitory action on Rac1 GTPase activity. I have now confirmed and characterized a novel interaction of Dok-4 with Arap3, a GAP with specificity for the Rho GTPases RhoA and Arf6.

I transiently transfected HEK293T cells with tagged versions of Arap3 and Dok-4, with or without the Src kinase domain (Src SH1) and performed co-immunoprecipitation (co-IP) studies using different combinations of antibodies. My results show that the Dok-4 PTB domain (aa 131-246) is sufficient to interact with Arap3. Importantly, in the presence of the Src kinase domain, Arap3 became tyrosine phosphorylated and its interaction with Dok-4 was markedly enhanced. Finally, Dok-4 constructs containing a mutation at a critical glycine residue of the PTB domain (G207A mutant) were greatly impaired in their ability to bind Arap3, confirming that canonical PTB function is involved in the Dok-4/Arap3 interaction, as my lab has recently found for the Dok-4/Chn2 interaction.

In conclusion, Dok-4 interacts with at least two distinct inhibitors of Rho GTPases (Chn2 and Arap3) through a tyrosine kinase-regulated mechanism involving its PTB domain. While the functional impact of the Dok-4/Arap3 interaction remains to be defined, these findings suggest that regulation of Rho-GTPase activity may be a key mechanism of Dok-4 inhibitory action. This may have important implications of epithelial diseases involving normal or abnormal tyrosine kinase and Rho GTPase activity, such as acute kidney injury, nephrotic syndrome and cancer.
B-11 The role of cancer-stem cells in malignant melanoma

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**Background:** Melanoma is a type of cancer that develops from the pigment-containing cells called melanocytes. It occurs mainly in the skin, but rarely in the eye, mouth and intestines. Melanoma is highly metastatic and therapy-resistant. Some subpopulations of melanoma cells exhibit cancer stem cells (CSCs) features including tumor-initiation, self-renewal and hierarchical differentiation. CSCs have been reported to express a variety of surface markers (e.g. CD133, CD271, CD44, CD166, ABCB5, etc) and intracellular markers (e.g. ALDH1, JARID1B, nestin, etc). Isolation of CSCs can be done by sorting the cells based on the expression levels of CSCs markers. Our project is to isolate CSCs and study growth behavior to understand the role of CSCs in melanoma metastasis.

**Aims:**
1) Isolate subpopulations of melanoma cells that display “high” and “low” stemness using extracellular and intracellular markers.
2) Characterize cell growth behavior of “high” and “low” stemness cell subpopulations.

**Method:** Isolation of CSCs will be performed on two primary (WM115 and A375) and two lymph node metastatic (WM266.4 and A2058) human melanoma cells by using established flow cytometry cell sorting. Cells are sorted based on the expression levels of extracellular CD44 and intracellular ALDH (Alde-Fluor). To assess the growth potential of “high” (ALDH high/CD44+) and “low” (ALDH low/CD44-) stemness, we will perform a) a clonogenic assay in soft agar and b) a spheroid growth assay to test the anchorage independent growth. Migration and invasion assays will be performed using the Inucyte live-cell analysis system.

**Expected Results:** We expect that “high” stemness (ALDH high/CD44+) melanoma cells display increased anchorage independence, migration and invasion, which will indicate that melanoma cells with increased stemness exhibit a more metastatic phenotype.
Waiting Time Visualizations for Patient Appointments in the Opal Patient Portal

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\textbf{Introduction:} In 2014, the Opal project began with the goal of improving patient satisfaction through sharing of appointment data and waiting times with patients. These data would allow patients to set reasonable waiting time expectations and therefore use their personal time more efficiently, while simultaneously improving their understanding of and willingness to accept delays. Since 2014, Opal has become much more than just a tool to share waiting time data but the importance of this aspect of the project remains undiminished.

\textbf{Objective:} The goal of this summer’s research project was to continue work on the appointment and patient waiting times feature within Opal, including debugging and reconfiguring the waiting time visualizations so that they may be included in the production version of Opal.

\textbf{Methods:} The original project built data structures that could handle and process huge amounts of data very quickly. In the present project, we analyzed the minutiae of that process to solve logical errors and inconsistencies so the feature would correctly process data. To isolate errors, test databases with small amounts of data were used. Through testing individual code modules, building flow charts, and creating mock patients and appointments to represent edge cases, limitations in the code were caught and fixed.

\textbf{Results:} There are two components to the original visualizations. The first is My Waiting Time, a feature that retrieves and displays patients’ historical waiting times, categorizing them as too early, on time, or late, and showing whether the reason for waiting was attributed to the hospital or the patient’s early arrival. The original visualization didn’t account for the appointment’s actual start time as opposed to scheduled time. This was corrected in the current project. The second component is Appointment Historical Delays, a feature that retrieves and summarizes a given appointment type’s historical waiting times. This shows patients how long they may expect to wait based on previous patients’ waiting times for the same appointment type at the same time. Bugs were fixed in both components to accurately display the waiting time graphs. The components were further modified so when data are missing, the code continues processing results, instead of freezing.

\textbf{Discussion:} The next step is to merge waiting time visualizations into the production version of Opal and to test them with larger amounts of data. The code was built for use with a database of 350,000 appointments, but must be tested for speed and performance.
B-13 Identification of tumor and healthy regions on biopsy slides by using machine learning algorithms

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Background: Tissue response to ionizing radiation varies with different factors, such as the size of the cells and their nuclei, as well as their DNA content. Inter patient variations in nuclei sizes are observed between tumor and healthy cells for the same type of tumor, and between different types of tumors. Hence, dose to the cell’s nucleus is a relevant quantity to consider in radiotherapy given the importance of DNA damage. However, it is not yet well known how morphological and chemical variations can affect the energy absorbed by the different compartments in the cells. Previously, we have developed algorithms to build morphologically realistic 3D cellular geometry models. These models are used to study dose response due to the cell/nuclei size distribution using a Monte Carlo based dose calculation software developed by our group. The models are created by deriving cell and cell nuclei size distributions from 2D histology samples. The histology slides are firstly stained before the tumor and healthy regions are contoured by a pathologist. Due to the huge workload of the pathologists, few histology slides are contoured, thus researches in this field are restricted and limited by the small dataset available.

Aim: The aim of this project was to develop machine learning algorithms to identify tumor and healthy regions on histology slides in order to remove the dependency of a pathologist for contouring those regions.

Methods: A deep learning algorithm is created using Python and Tensorflow. As the final output of the algorithm needs to show the segmentation of the original image into different regions, a convolutional neural network (CNN) is being built based on the architecture of U-net, a model used for biomedical image segmentation developed in the University of Freiburg in Germany. The CNN is trained to identify tumor and healthy regions using the slides contoured by the pathologist as ground truth. Due to the low number of slides available, random patches of smaller sizes have been extracted from each slide to increase the training images fed into the network.

Results & Conclusion: Once the network is written, the supervise learning of the CNN will actually begin. Data augmentation, like rotations and elastic deformations, will be performed to increase the training dataset, and other contoured slides from the pathologist will likely be available soon for training. Afterwards, this will allow new slides (not contoured) to be segmented by the algorithm and used in current researches.
Characterization of the role of ALFA-1 in C. elegans vulva induction and epidermal growth factor signaling

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Epidermal Growth Factor Receptor (EGFR) signaling plays a crucial role in the pathogenesis of human cancers as it promotes cell growth and proliferation. EGFR signaling is well modeled in the nematode Caenorhabditis elegans, in which the epidermal growth factor (EGF)-like ligand LIN-3 activates the LET-23^{EGFR} receptor in vulva precursor cells (VPCs) to initiate vulva induction. In wild-type animals, exactly three of six VPCs are induced, but defects in signaling can result in VPC over- or under-induction; as such, the number of induced VPCs provides a quantitative readout of EGFR signaling. Basolateral localization of LET-23 is essential for signaling and promoted by a tri-complex comprising LIN-2, LIN-7, and LIN-10; each constituent is critical, as the loss of any of these components leads to an under-induced vulvaless phenotype. In contrast, basolateral localization is negatively regulated by Arf GTPases and their associated guanine nucleotide exchange factor (GEF), AGEF-1. It has been shown that mutations in agef-1 lead to extra-embryonic accumulation of yolk in embryos, indicating defects in yolk trafficking. In addition, agef-1(-) mutations suppress the lin-2(-) mutant vulvaless phenotype, confirming pathway interaction. Similarly, mutations in alfa-1, the C. elegans ortholog of the human C9orf72 gene (the most common genetic driver of Amyotrophic Lateral Sclerosis (ALS)), also results in this yolk ‘blob’ phenotype. As such, we hypothesize that ALFA-1 plays a role in vulva induction and interacts with components of the EGFR pathway. We have generated alfa-1(-); lin-2(-) double mutant strains to assess whether the alfa-1(-) mutation suppresses the lin-2(-) vulvaless phenotype similarly to an agef-1 mutation. We will analyze and quantitatively assess vulva induction in alfa-1(-); lin-2(-) strains. Together, this may elucidate a new regulator of LET-23^{EGFR} trafficking and provide preliminary data for the role of ALFA-1 in C. elegans EGFR signal transduction.
B-15 The role of sex hormones in plaque instability in men and women with severe carotid atherosclerosis

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**Background:** Ischemic strokes are one of the leading causes of death in men and women. Carotid atherosclerosis occurs when fatty material accumulates and forms a plaque in the arteries that feed blood to the brain. Plaques can be characterized as either stable or unstable, where unstable plaques are more likely to rupture and cause strokes. Men tend to have more unstable plaques as compared to women; however, women have worse recovery and increased mortality rates post-stroke. Sex hormones are thought to affect the vasculature differently in men and women. Specifically, estrogen has been observed to have a protective role against cardiovascular disease in pre-menopausal women; however, this protection is diminished with age. We hypothesize that higher levels of estrogen are linked to more stable plaques in women and higher levels of testosterone are linked to less stable plaques in men, therefore demonstrating that sex hormones play a different role in plaque instability in women and men. The role of sex hormones in plaque instability will be investigated at the plaque level and in blood in men and women with severe carotid atherosclerosis.

**Methods:** Men and women undergoing carotid endarterectomy were recruited at the MUHC. Plaques were recovered, histologically classified as either stable or unstable, and were separated into 4 groups: women stable/unstable and men stable/unstable. Immunohistochemistry was performed with antibodies against estrogen receptor alpha (ER-\(\alpha\)), estrogen receptor beta (ER-\(\beta\)), G-protein coupled estrogen receptor (GPER), and androgen receptor (AR) on 10 plaques from each representative group. The percent area stained relative to total plaque area, and staining intensity of sectioned plaques are being digitally quantified using the Image-Pro Premier software. Liquid chromatography mass spectrometry is being used to quantify the amount of circulating sex hormones in the blood.

**Results:** The antibodies have been optimized on prostate, cervix, and breast tissue. To date, testosterone, androstenedione, and DHEA have been detected in the blood. Ongoing analysis is being performed with estradiol. Significantly higher levels of testosterone were observed in men with unstable plaques as compared to men with stable plaques (P<0.05). Additionally, we have observed the presence of ER-\(\alpha\) and GPER and the absence of ER-\(\beta\) and AR in carotid plaques. Expression has been observed specifically in macrophages, foam cells, endothelial cells, and smooth muscle cells.

**Conclusion:** In determining the effect sex hormones have on plaque stability, we may be able to design hormone-specific therapies for men and women with unstable plaques.
B-16 A Characterization of Abnormal Growths of the Neural Ectoderm in C-CPE-Treated Chick Embryos

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Although fortifying flour with folic acid and taking folate in prenatal vitamins has considerably reduced the rate of NTDs, neural tube defects (NTDs) still affect around 1 in 1,000 live births and are the second most common birth defect, after cardiovascular defects. Defects in neural tube closure lead to spina bifida and anencephaly. Claudins are a family of proteins that dictates the permeability of tight junctions, the most apical cell-cell junction. Using C-CPE, which depletes Cldn3, -4 and -8 from tight junctions, the Ryan lab demonstrated that these claudins are required for neural tube closure. A subset of C-CPE-treated embryos also had tumour-like growths in the neural ectoderm and a misshapen notochord, in addition to their open NTDs. The origin of the cells within the abnormal growths is unknown, as are their expression profile and characteristics. I hypothesize that they originate from neural crest cell precursors in the neural ectoderm, and that the cells within the abnormal growths exist in a transient state between epithelial and mesenchymal. Preliminary studies has shown a similar labelling for Sox2 in the abnormal growths as the neural ectoderm. The mRNA expression pattern of Sox2, Shh and AP2a were analyzed using whole-mount in situ hybridization. The penetrance of the phenotype will be assessed, and the abnormal growths’ volume and circumference will be measured, as well as the notochord’s size. These analyses will determine the characteristics of the abnormal growths and of the notochord.
Mucopolysaccharidoses (MPS) are a family of recessive lysosomal storage diseases that occur due to a lack of specific enzyme necessary to break down glycosaminoglycans (GAGs). As a result, GAGs accumulate in various organs and ultimately lead to progressive organ failure. Due to this understanding, GAGs have since been used as biomarkers, and their levels in urine form the basis for the currently available diagnostic test for MPS. However, GAGs alone were shown to be inefficient prognostic markers for MPS, due to the variations in levels seen with factors such as age. GAG accumulation is suggested to stimulate the toll-like receptor 4 (TLR4) signalling pathway due to structural similarities with TLR-4 agonists. It is believed that activation of these cellular signaling pathways is what leads to the release of pro-inflammatory cytokines and activation of ceramides. Previous studies have in fact demonstrated increased levels of inflammatory cytokines and ceramide, a class of sphingolipids that play a critical role in inflammatory and pathological processes, thereby suggesting their involvement in the MPS symptoms. With our unique access to a large cohort of MPS patients, we aim at investigating the levels of cytokines, ceramides, and GAGs in MPS patient serum, using Quansys and novel liquid-chromatography tandem mass spectrometry methods (LC-MS/MS). Thus far, we have analysed levels of different species of ceramides in serum and found differences in levels between patients and healthy controls, suggesting the potential role of specific ceramide species as biomarker. We also refined the method for serum GAG analysis, and are currently analyzing cytokine levels and quantifying GAGs in blood of MPS patients. Ultimately, in the coming weeks, this will allow us to evaluate the relationship between serum levels of cytokines, ceramides, GAGs and the clinical phenotype of MPS patients in order to identify specific biomarkers for diagnosis of MPS, to monitor therapy, and to further understand the pathophysiology of these diseases.
Genetic analysis of a RECQL variant c.1138A>T [p.Lys380*] in French Canadian breast cancer cases with familial breast cancer

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Background: The discovery of high risk breast cancer (BC) predisposition genes such as BRCA1 and BRCA2 has provided the scientific community with invaluable knowledge about familial breast cancer. Despite this, the genetic causes of some familial BC cases remain unknown. Recently, RECQL has been proposed as a BC predisposition gene. However, other studies have also shown that RECQL variants show little to no association to BC risk. Previously, the c.1138A>T RECQL variant was found in whole exome sequencing (WES) data from a French-Canadian (FC) bilateral BC case also positive for the BRCA2 c.3170_3174delAGAAA [p.Lys1057ThrfsTer8] pathogenic variant. Subsequently, we filtered all genetic variants from DNA repair genes from that case using in silico tools. Only DNA repair genes were analyzed because alterations in these genes are prevalent in hereditary and somatic BC. Notably, variants in PALB2, RAD54L, SMC5, and OGG1 remained after filtration. Here, we aimed to analyze the spectrum of germline RECQL variants in BC cases regardless of BRCA1/BRCA2 carrier status. All cases were of FC descent in order to investigate possible founder RECQL mutations due to common ancestry. We hypothesize that when in the presence of other high-risk BC predisposing genetic variants, mutations in germline RECQL further increase BC risk.

Methods and results: The mutational spectrum of RECQL was examined from WES data of 58 BRCA1/BRCA2 positive and 18 BRCA1/BRCA2 negative BC cases. Twenty RECQL variants were found in BRCA1/BRCA2 positive cases and 13 in BRCA1/BRCA2 negative cases. However, no variants from either cohort remained after filtration, meaning that they classified as non-pathogenic according to our variant filtration pipeline. Next, to assess the effect of c.1138A>T on BC risk, 88 familial BC cases, regardless of BRCA1/BRCA2 mutation status, are being genotyped using Taqman® for c.1138A>T.

Conclusions: Results to date show that RECQL variants do not seem to significantly associate with BC, regardless of whether cases are BRCA1/2 positive or negative. After the genotyping of the 88 familial BC cases, if c.1138A>T is present, it would indicate that this variant could be associated with BC risk. Nevertheless, if c.1138A>T is not present, it would not indicate that the variant is not associated with BC risk due to the small sample size. Overall, our results contribute to the general understanding of the mutational spectrum of RECQL in BC.
**C-19 Involvement of Arf1/COPI Machinery on Lipid Droplet Dynamics**

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**Introduction:** Lipid droplets (LDs) are phospholipid-monolayered storage organelles for neutral lipids, playing an important role in lipid and energy homeostasis. Cells usually have two populations of lipid droplets. The larger LDs, several microns in diameter, act as reservoirs for metabolic energy and precursors. In addition, smaller nano-LDs, less than a micron in diameter (~60nm), have been reported to bud from larger LDs. Their high surface-to-volume ratio facilitates fusion with the ER bilayer. Members of the Arf1/COPI machinery have been identified in literature using unbiased genome-wide screens in model systems (e.g. drosophila) to be necessary for LD morphology, unlike other secretory proteins such as COPII and clathrin. It was first shown that Arf1, the Arf1 GEF GBF1, and numerous other COPI machinery can be found on LDs in proteomic and cell biological studies (Beller et al., 2008; Guo et al., 2008). Most recently, GTP-bound Arf1 and COPI proteins were shown to interact with monolayer interfaces in vitro using a phospholipid-covered oil-water interface (Thiam et al., 2013). The observed budding of nano-LDs from this interface suggests a new model in which Arf1/COPI machinery functions at LDs. We have previously shown that the ARF GTPase Activating Protein 1 (ARFGAP1) transiently associates with LDs in some hepatocytes from human liver tissues and that the overexpression and knockdown of ARFGAP1 has an effect on LD formation (Gannon et al., 2014). Here, we investigate a putative COPI interactor in the context of lipid droplet and their dynamics.

**Methods:** Gene expression in fibroblast cells with fluorescently labeled protein of interest (HEK293) was induced with tetracycline, and closely followed by oleic acid and bovine serum albumin loading at various concentrations (0-200µM). Cells were fixed and stained against marker enzymes of various organelles as well as Bodipy and/or Nile Red staining of lipid droplets. Changes in lipid droplet diameter and area were quantified. Experiments were repeated with siRNA knockdown of COP components.

**Results:** Experiments and analyses are currently underway and will be presented on August 13.
Shape recognition in perfusion MRI as an early marker of treatment response in breast cancer

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Purpose: In this work, we present an ongoing investigation of a shape-recognition analysis method for dynamic contrast enhanced (DCE)-MRI that uses elements of quantitative compartment models. In our past work, the approach was used to assess tumour perfusion and the mean-non-zero weight of each shape accurately reflected pathology-confirmed treatment response in a dataset from breast cancer patients treated with chemotherapy. The validity of the method will be tested on an independent dataset. In addition, a method for automatic contouring of tumour regions-of-interest (ROIs) is being implemented to avoid manual contouring.

Methods: Dataset A (N=10 patients) was reanalyzed to ensure that observations were reproducible. A semi-automatic contouring approach was designed based on a combination of image thresholding and very approximate manual contouring by an untrained observer. The resulting ROIs were compared to expert contours using detection sensitivity and Dice similarity coefficients (DSC). Semiautomatic contours were also defined for independent dataset B (N=31 patients).

Results: Results from dataset A were reproduced independently using the expert contours. Attempts at semi-automatic tumour contouring have yielded ROIs that disagree with the expert contours (range of DSC = 0.0853 to 0.8060). Using these semi-automatic ROIs, the initial results obtained with dataset A were not reproduced. Development of semi-automatic tumour contouring is ongoing. Analysis of dataset B awaits an improved set of tumour contours.

Conclusions: Shape recognition analysis of DCE-MRI data may predict treatment outcome. The definition of tumour contours influences the performance of the method. So far, semi-automatic contouring based on a combination of thresholding and manual intervention does not agree with expert contouring. Once an appropriate contouring method is developed, we will test the hypothesis that the mean-non-zero weights from the shape-recognition method are related to treatment outcome in the independent dataset.
C-21 Investigating the high fat diet-induced deregulation of DNA damage response in MYC-driven prostate cancer

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Prostate cancer (PCa) is the most common nondermatological malignant tumour diagnosed and is ranked as the third cause of death by cancer in Canadian men. Epidemiological studies indicate that the etiology of PCa can be affected by numerous factors, including environmental factors such as a diet rich in saturated fats (HFD), suggesting a key role of diet in the incidence of PCa progression and mortality. Thus, it is important to understand the mechanistic link between HFD and PCa progression. Data derived from dietary manipulation of a MYC-driven murine PCa model showed that tumours grown in mice maintained on a HFD were more aggressive and, even before the appearance of a HFD-dependent phenotype, had elevated levels of gH2A.X and other markers of DNA damage, compared to tumours from mice fed a control diet (CTD). Therefore, we hypothesize that the metabolic alterations associated with HFD dysregulate the DNA damage response (DDR) machinery of PCa tumour cells, inducing an accumulation of unrepaired double-strand breaks (DSBs) that results in genomic instability and ultimately enhances PCa progression. To understand which specific pathways of the DDR are affected by diet, we treated MyC-CaP cells, a murine PCa cell line overexpressing the oncogene c-MYC, with culture media supplemented with plasma collected from mice fed either a CTD or a HFD. After 24 hours of treatment, cells were lysed for western blot analysis to compare the expression of various mediators of the DDR upon different dietary conditions. Preliminary results indicate an upregulation of the ATM/Chk2/p53 pathway and a down-regulation of the ATR/Chk1/CDC25 arm of the DDR in cells treated with plasma from HFD-fed mice, suggesting that HFD increases DNA damage by deregulating the DDR pathway. To determine if this effect is specific to MYC-driven PCa cells, the same experimental design was applied to a Pten null murine PCa cell line stably expressing a tamoxifen-inducible c-MYC transgene. Western blot analyses indicate that HFD-plasma induces DDR also in this cell model, but the effect is further enhanced by MYC-overexpression. We are currently performing cell cycle analysis and β-galactosidase assays on plasma-treated cells to determine if HFD alters cell cycle and/or trigger senescence, respectively. If such phenotype is observed, we will test the effect of senolytic drugs, designed to clear senescent cells, in combination with dietary manipulation to partly revert the HFD-induced PCa aggressive phenotype.
C-22  Biomarkers for Mucopolysaccharidoses

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Mucopolysaccharidoses (MPS) are a family of recessive lysosomal storage diseases that occur as a result of lack of a specific enzyme necessary to break down the glycosaminoglycans (GAGs). GAGs accumulate in various organs of patients and lead to numerous symptoms visible in the whole body. Some of the clinical features are macrocephaly, cloudy corneas, spinal chord damage, and hernias. MPSs have a strong prevalence in Quebec, especially for type IVA (Morquio A syndrome), giving us access to a large cohort of MPSs patients at the MUHC (MPSI n=3; MPSII n=3; MPSIIIA n=2; MPSIVA n=36, and MPSVI n=13.) GAGs accumulation has been suggested to stimulate the toll-like receptor 4 (TLR-4) signalling pathway due to structural similarities with TLR-4 agonists, leading to increasing levels of ceramides, and other metabolic disruptions suggesting ceramide involvement in the MPS symptoms. In this study, two potential classes of serum biomarkers were investigated: ceramide and proteins. Three classes of ceramides were analyzed using a novel liquid-chromatography tandem mass spectrometry method (triple quadrupole). Intact serum proteins were investigated via a top-down proteomics method using an LC/MS followed by LC-MS/MS (LC-qTOF). Our results reveal an increase in hexosyl-ceramide species in most of the MPSs patients, compared to age-matched healthy controls. As well, Fibrinogen α and γ were found to be over abundant in MPS serums, particularly Morquio A patients. Our results allow better understanding of the pathophysiology and etiology of MPS diseases, as well as propose new therapeutic targets for diagnosis, treatment follow up and prognostic information for patients and families.
Tuberculosis (TB) remains one of the world’s leading causes of death, affecting nearly 1.8 billion individuals according to the World Health Organization. South Africa suffers from one of the world’s most serious epidemics, which is characterized by high rates of incidence, multidrug-resistance, and TB/ HIV co-infection. It poses major fiscal and administrative challenges for the public and private medical sector in a country struggling with a history of corruption, stigma, and political discord. This study based in Cape Town, South Africa, utilizes Standardized Patients (SP) to assess quality of care in tuberculosis management in the private sector. Studies have shown that many individuals still refer to the private sector for services freely available in the public sector; however, the quality of care in the private sector is widely understudied. Standardized patients are actors who are extensively trained to present characteristic TB tracer symptoms, including TB/HIV co-infection and multi-drug resistant TB, while following a carefully-developed script. SP’s visit consenting private practitioners and capture essential elements of the interaction through post-interaction surveys. The “know-do gap” is subsequently measured between provider knowledge and practice. This standardized patient methodology may help to pinpoint the diagnostic, clinical, and behavioral patterns which influence patient loss throughout the healthcare cascade. It is imperative to continue analyzing consultation data as well as patient preferences to gain further insights into ameliorating TB management in South Africa.

This is a collaborative study between McGill University and the Human Sciences Research Council (HSRC) funded by the Bill & Melinda Gates Foundation.
C-24 The Role of las Quorum Sensing on the Interactions of Intracellular Pseudomonas aeruginosa and Airway Epithelial Cells

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Introduction: Pseudomonas aeruginosa (Pa) is a ubiquitous gram-negative opportunistic pathogen that causes severe persistent lung infections in compromised hosts such as patients with the inherited disease Cystic Fibrosis (CF). As it adapts to the host lung, Pa undergoes many genotypic and phenotypic adaptive changes such as that of the loss of function of lasR, the gene which encodes the LasR transcriptional activator of quorum sensing (QS). QS controls the expression of hundreds of genes, many of which are involved in pathogenicity and host-pathogen interactions. Lung infections with loss of function lasR Pa variants are associated with accelerated lung decline in CF patients and a hyperinflammatory host response in murine chronic lung infection models. Recent data from our lab suggests that Pa, while classically considered an extracellular pathogen, can be internalized within airway epithelial cells. This intracellular lifestyle may allow the bacteria to evade the host immune system and extracellular antibiotics such as aminoglycosides which are commonly used in the clinic. We are interested in understanding the potential roles of lasR on the intracellular lifestyle of Pa in the airway epithelium.

Methods and Results: We used a tobramycin protection assay with BEAS-2B and CFBE cell monolayers alongside primary cells that were differentiated at the air-liquid interface as a model of internalization and early intracellular persistence. Seven Pa early clinical and laboratory wild-type and isogenic lasR-deficient strain pairs were co-incubated with epithelial cells for 4h or 24h. At the 4h time point, tobramycin was added to the cell media to kill extracellular but not intracellular bacteria. Epithelial cells were harvested at each time point and analyzed for cytotoxicity and intracellular bacterial load. We found that while in BEAS-2B cells there was no clear trend towards more or less cytotoxicity induced by the lasR-deficient strains, four of the seven strains were significantly more intracellularly abundant after 24h and two were trending towards an increase. These results were repeated in a CFBE cell-line model with both of the selected pairs at 4h and 24h time points.

Conclusion: Loss-of-function lasR mutant Pa strains are internalized by bronchial epithelial cells to a greater degree than their wild-type parental strains. In some strain backgrounds, this leads to greater intracellular bacterial persistence over time. What LasR-dependent mechanism(s) contribute to this increased internalization remains to be determined. Future studies will include adhesion assays to epithelial surfaces and validation in naturally-occurring clonally-related lasR mutants.
D-25  An analysis of the anatomical changes of the rectum and bladder in prostate cancer patients over the course of radiation therapy

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Introduction: Radiation therapy (RT) is used as a curative treatment for prostate cancer. Although RT is highly effective in eliminating prostate cancer cells, high radiation dose to normal surrounding structures—namely the bladder and rectum, can cause acute and late side effects for prostate cancer patients such as reproductive, rectal and urinary problems. An RT treatment plan is created based on an initial computed tomography (CT) scan to prescribe the appropriate dose to the planning target volume (PTV) for 20 days of treatment while limiting exposure to the rectum and bladder. Although the treatment plan takes into account the possible movements of the prostate gland within the PTV, it cannot predict the filling of the bladder, nor the distension of the rectum. These movements of the normal tissues may expose them to higher doses of radiation than planned.

Objective: The goal of this project is to show that the dose distribution calculated for prostate cancer patients at the outset of treatment is not accurate for the following days of treatment due to the daily changes in the shape and position of the rectum and bladder.

Methods: Contouring of the rectum and bladder on the cone beam CT (CBCT) scans of 25 prostate cancer patients was done using the Eclipse Treatment Planning system (Varian Medical Systems, Palo Alto, CA). Before contouring, the correct CBCT images needed to be assigned to the correct treatment days. Next, the CBCT images were registered with the original planning CT and they were assigned to their correct treatment fractions. The couch and body contours were added. Finally, the rectum and bladder were contoured.

Results: As of July 17th 2019, 5 patients have both the rectum and bladder contoured while the remaining 20 patients have the rectum contoured only. 2 out of the 25 patients have 19 days of CBCTs instead of 20 days. It was found that not only does the shape and position of the rectum and bladder change daily, but the superior and inferior limits of these organs shift as well.

Discussion: To limit rectal and urinary toxicities, we need an automated procedure or more resources to do frequent dose calculations instead of relying on a single initial pre-treatment CT scan. Future work will involve using the data generated in this project as input to a Deep Learning algorithm to automatically generate the contours of the bladder and rectum to speed up the process.
D-26  Primary stability measures of bone anchored hearing implants installed in human cadaveric bones

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Bone anchored hearing implants loss due to impeded stability occur more frequently in children, sometimes without apparent causes, and could extrude at any time after placement. The success of bone anchored hearing implants greatly relies on primarily stability achieved from the initial installation of the implant screw. Histomorphometric evaluation and mechanical testing provide valuable information about this implant anchorage. However, these tools cannot be applied in the surgical or clinical setting. Recently, Resonance Frequency Analysis (RFA) and Advanced System for Implant Stability Testing (ASIST) have been proposed as objective and non-invasive ways to measure implant stability. The relationship between primary stability assessed by the RFA and ASIST was analysed. The influence of implant design and patient related factors such as skull bone microarchitecture and quality were investigated. There is minimal effect of changes of implant characteristic such as abutment length on the ASIST coefficient value; however, RFA is influenced by abutment length. Compromised bone deleteriously affected the primary stability as assessed by the novel tools and conventional testing methods. This research presents a laboratory evaluation of the RFA and ASIST to determine the stability of Oticon Medical Ponto bone anchored hearing aid system. The ASIST method is able to isolate the interface properties from the overall system and the measurement is independent of attached components if threshold shifts are used. Absolute RFA values should not be interpreted individually and threshold shifts from baseline should be derived in individual patient in a population over time. After abutment replacement, RFA trends from baseline cannot be interpreted if the abutments differ in length.
D-27 Ontogeny of macrophages dictate a unique metabolic profile with a distinguished anti-viral immunity against IAV infection

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Despite the world-wide application of vaccination and other anti-viral interventions, Influenza infection remains a persistent threat to human health. Virulent Influenza A viruses (IAV) are the most clinically relevant to humans, causing lower respiratory infections associated with uncontrolled host inflammatory responses that lead to high morbidity and mortality. The exact mechanism(s) of immune dysregulation prompting massive immunopathology is poorly understood; however, it has been suggested to be a consequence of innate immune evasion by viruses. Pulmonary macrophages (Mφ) are critical mediators of the antiviral response to IAV through the production of a key antiviral cytokine, type I interferon (IFN-I). Moreover, embryonically-derived alveolar Mφ (AMφ) and monocyte-derived interstitial Mφ (IMφ) are the two main Mφ populations in the lungs. Recent studies indicated that macrophage effector functions are closely linked to their ontogeny and metabolic status. While AMφ rely on fatty acid oxidation, IMφ are glycolytically active and have increased antimicrobial activity. It has also been shown that IFN-I increases mitochondrial oxidative phosphorylation and anti-viral immunity of plasmacytoid dendritic cells to LCMV infection. In this study, we will investigate the link between pulmonary Mφ ontogeny, metabolism and antiviral activity following IAV infection in order to determine how Mφ-metabolic reprogramming impacts their effector functions, which may lead to identify a new therapeutic avenue to fight IAV infections.
Analyzing Muscle Loss and Myosteatosis after Surgical Prehabilitation in Lung Cancer Patients

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Lung cancer is the leading cause of cancer mortality worldwide. Cancer patients who undergo surgery are at risk for muscle loss and myosteatosis (fat infiltration in muscle), independent prognostic factors in many cancers including lung. Muscle health plays a central role in functional status and postoperative recovery such that it should be optimized before surgery. By utilizing a combination of nutritional and physical exercise interventions in the pre- and postoperative periods, muscle loss and myosteatosis may be attenuated. The objective of this study is to use a combination of CT and peripheral quantitative CT (pQCT) image analysis to measure changes in muscle volume and radiodensity of postural and limb muscles of non-small cell lung cancer (NSCLC) patients undergoing thoracic surgery, throughout a larger intervention trial. The study will enlist 66 patients with non-metastatic NSCLC and take place 4 weeks before and 8 weeks after surgery. Patients will be randomized to one of two arms, multimodal intervention (MM) or standard care (SC). The MM arm will receive moderate aerobic and resistance exercise training consisting of one supervised session and multiple home-based sessions per week. The MM arm will also consume a daily supplement containing leucine, whey protein, fish oil and vitamin D. Abdominal CT scans will be collected from medical charts before the intervention and 8 weeks after surgery. Images will be analysed at the L3 vertebra landmark to quantify cross-sectional areas of muscle and adipose tissue. Four pQCT scans of the non-dominant foreleg of each patient will be performed at 4 and 66% of the tibia length and will be assessed for muscle density and cross-sectional area. Independent t-tests will be used to determine the differences between myosteatosis and muscle loss in the two muscle regions at corresponding time points. Repeated-measures ANOVA will determine the effect of the intervention over time within and between groups. Correlations between muscle density and functional tests will be assessed. It is hypothesized that myosteatosis will be higher in the abdominal region, due to this area being surrounded by more visceral fat and being less utilized during physical activity compared to the legs. Myosteatosis and muscle loss are hypothesized to be lower in MM patients in comparison to the SC patients when assessed post-surgery. This study has the potential to uncover valuable knowledge about the pathogenesis of myosteatosis and muscle loss to better personalize prehab/rehabilitation and help increase quality of life for NSCLC patients.
Testing for the involvement of GIT1, GIT2, ARF1 and ARF6 in Congenital Mirror Movement Disorder

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Introduction: Congenital mirror movements (CMM) are characterized by the involuntary movements of one side of the body mirroring of voluntary movement from the contralateral side. CMM disorder results from abnormal wiring of the motor tracts (i.e. corticospinal tracts), and is thus considered a disorder of axonal guidance. It almost always has an autosomal dominant inheritance pattern with incomplete penetrance. Several genes causing CMM have been identified such as DCC and RAD51. However, approximately 65% of cases remain unexplained¹. The ARF1 and ARF6 genes encode ADP ribosylation factors (ARFs). GIT1 and GIT2 encode G Protein-Coupled Receptor Kinase-Interacting Proteins that are ARF-GTPase activating proteins which inactivate ARF1 and ARF2. These proteins play an important role in microtubule growth, vesicular trafficking, steering axonal growth cones and formation of lamellipodia and filopodia. Because of their involvement in axonal guidance, they represent interesting candidate genes in the pathogenesis of CMM.

Aim: To determine whether mutations in GIT1, GIT2, ARF1 or ARF6 are responsible for CMM disorder by screening these genes in a cohort of individuals with unexplained CMM.

Materials and Methods: We screened GIT1, GIT2, ARF1, and ARF6 in genomic DNA extracted from lymphocytes from 30 individuals with unexplained CMM. Previous sequencing of known CMM genes (DCC, RAD51, NTN1, ARHGEF7, DNAL4) did not identify any causal variants. Primers were designed using UCSC Genome Browser version February 2009. Patient exons were amplified by six multiplex PCRs with the Platinum Taq from Thermo Fisher Scientific. Amplicons were cleaned and pooled with AMPure XP beads and prepared for sequencing using the Nextera XT library prep kit. DNA was then sequenced on the MiSeq and analyzed by the bioinformatics platform.

Results: Screening for GIT1, GIT2, ARF1, and ARF6 in blood samples from 30 patients found no significant genetic variants.

Discussion and Conclusion: Congenital mirror movement disorder is less likely to be caused by mutations in GIT1, GIT2, ARF1, and ARF6 genes. Further investigation is required to discover the genes responsible for CMM.
D-30 Maternal ICU admissions at the MUHC and Impact of Advanced Maternal Age on Outcomes: Retrospective Chart Review

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Background: Severe maternal morbidity (SMM) necessitating intensive care unit (ICU) admission is rising. Advanced maternal age (≥ 35 years, AMA) is associated with SMM, but its impact on ICU outcomes is not clear.

Objectives: We aimed to describe characteristics of pregnant and postpartum women admitted to the ICU at our institution, and to evaluate the impact of AMA on length of stay, need for invasive intervention, and death.

Methods: We conducted a retrospective chart review of ICU admissions during, or within 42 days, of pregnancy, from January 1, 2006 to December 31, 2016. Impact of AMA on outcomes will be assessed with log binominal regression analysis.

Results: 205 women were admitted to the ICU during pregnancy or postpartum period. Analyses of the entire cohort are ongoing. We report here a descriptive analysis of a subset of patients (n = 97). Mean age was 32.5 ± 6 years; 39 (40.1%) had AMA. Most admissions (70.1%) occurred during the postpartum period. High prevalence of hypertensive disorders of pregnancy (19.6%) and gestational diabetes (13.4%) was noted. One third delivered prematurely (<37 weeks), 34% required emergent C-section, and rate of intra-uterine fetal demise was high (4.1%). Reasons for ICU admission were obstetrical (41.2%), medical (20.6%), and surgical (2.1%). Mean length of ICU stay was 2.6 ± 3.5 days, with 43.3% exceeding 1 day. The vast majority (72.2%) of patients required invasive interventions. No deaths recorded.

Conclusion: The majority of maternal ICU admissions are in the postpartum period in women with at least one maternal or fetal complication. Ongoing analyses of the entire cohort will further characterize the sample based on comorbidities, explore outcomes according to maternal age, and describe the encountered cases of maternal death.
D-31 Establishing a model of Pseudomonas aeruginosa infection in zebrafish larvae

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A frequent feature of cystic fibrosis (CF) is chronic infection of the lungs by Pseudomonas aeruginosa. While treatment strategies exist, such as early antibiotic treatment with Tobramycin, this is not sufficient to eradicate the bacteria in several CF patients. However, whether the failure to eradicate is linked to the bacteria, the host or an interaction of both is not known. Zebrafish larvae provide a useful vertebrate model not only due to their transparency but by providing a useful system with which to study the innate immune response. In order to investigate whether Tobramycin is insufficient in these patients due to an interaction between the host and bacteria, our objective is to establish an in vivo model of P. aeruginosa infection in zebrafish larvae.

Following preliminary experiments on the impact of zebrafish culture medium on P. aeruginosa growth, zebrafish were treated with sodium hypochlorite solution 6 hours post fertilization (hpf) to sterilize the chorion and hinder the establishment of the zebrafish’s endogenous microbiota. Zebrafish were then infected with a GFP labelled lab strain of P. aeruginosa by adding bacteria directly to the zebrafish culture medium. Confocal images of the zebrafish embryos were taken at 2 dpf and the zebrafish were then washed at 3 dpf to remove chorion debris and bacteria remaining in the zebrafish culture medium. At 6 dpf, the zebrafish larvae were anesthetized with tricaine and more confocal images were taken. Confocal images demonstrated that at 2 dpf, P. aeruginosa established a surface infection on the zebrafish larvae, which could also be seen in the confocal images taken at 6 dpf.

This preliminary model serves as a basis for establishing a model of persistent P. aeruginosa infection in zebrafish, which could later be used to assay factors that influence P. aeruginosa persistence. Future experiments could also be done to look at the response of P. aeruginosa infected zebrafish to antibiotics, such as Tobramycin, in order to better understand why Tobramycin is insufficient in treating a proportion of CF patients.
Assessing skin tolerability scales of percutaneous bone-anchored hearing implants using the Holgers classification, IPS, and Tullamore scales.

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Percutaneous bone anchored hearing implants (BAHI) imply a continuous breach in the skin surrounding the temporoparietal skull bone region. To compensate for this breach, immunological mechanisms in the subcutaneous tissue surrounding the implant become more active. A grading system to standardize the reporting of such soft tissue reactions was introduced by Holgers et al in 1988. Since then, improvement of surgical techniques and innovations of implant design have led to less invasive surgeries, resulting in fewer adverse skin reactions. Several reports and clinical experience mention that the Holgers classification is outdated. Thus, new skin tolerability scales have been proposed, but their accuracy, in comparison to the Holgers classification, have yet to be well established. The primary objective of this study was to determine and to compare the variability amongst scorers for three skin tolerability scales used in post-operative assessment of bone anchored hearing implants. A group of ENT surgeons, residents, and health professionals who have experience with bone anchored hearing implant surgery graded twelve BAHI skin reaction images using three scales: the Holgers classification, the IPS scale, and the Tullamore scale. To determine the variability and to compare outcomes of these skin tolerability scales, Cohen’s kappa value for inter-observer agreement was calculated for each image and for the complete dataset. Moreover, the level of clinical experience of scorers was considered, as its effect on inter-observer agreement was evaluated. The Cohen’s kappa value was low for all three skin tolerability scales. No significant difference demonstrating less variability of a scale over another was detected. Experience with bone anchored hearing implants did not affect variability scores. Adherence to the three classification scales is generally poor for all three skin tolerability scales amongst scorers. Nonetheless, the endorsement of these scales is recommended for BAHI follow up care. Improved classification scales are needed to adequately address skin reactions and the recommended therapeutic and follow up regimen per reaction score.
E-33 Examining HIV transmission clusters among newly-diagnosed asylum seekers in Montreal, Quebec

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Background: Migrants represent an increasing proportion of people living with HIV in Canada. In recent years, Montreal has witnessed a change in its local HIV epidemiology. In 2015-2016, people from HIV-endemic countries represented 15-20% of all newly declared HIV infections, compared to 51% in 2017. Asylum seekers who are newly diagnosed with HIV through the Immigration Medical Exam (performed within 30 days from arrival) represent a key population for whom there is a paucity of data regarding HIV transmission dynamics following arrival in Canada.

Objectives: We aimed to identify and characterize HIV infection transmission clusters among newly-diagnosed asylum seekers using phylogenetic analyses. We hope to track linkage of viral variants at a population-level with the overall goal of improved HIV surveillance among this key sub-population in Montreal. We hypothesized that the domestic spread of HIV transmission within the province can be detected using this method.

Methods: Retrospective chart reviews of newly-diagnosed asylum seekers linked to HIV care between June 1, 2017 and December 31, 2018 at the McGill University Health Centre (MUHC) were performed. Phylogenetic trees were reconstructed using Neighbor-joining and Maximum Likelihood analysis. Transmission clustering of linked viral sequences was based on strong bootstrap support (>98%) and short genetic distance (0.01–0.05 substitutions/site) or posterior probabilities. Heterosexual (HET) and men who have sex with men (MSM) clusters were identified.

Results: Sequences were obtained from 83 patients at the MUHC. Among these, 36 originated from Haiti; HIV subtypes included B (n=34), F1 (n=1) and CRF02_AG (n=1). There were three Haitian HET subtype B clusters. Nineteen individuals arrived from Nigeria; HIV subtypes included G (n=3), CRF02_AG (n=13), CRF06 (n=1), CRF09 (n=1) and C (n=1). There were two Nigerian HET clusters; one each of subtype G and CRF02_AG. There were two Latinos with subtype B and the remaining 26 persons arrived from Africa with various non-B subtypes. There was one Burundi HET subtype C cluster. Two subtype B clusters showed spread to/from an MSM in Quebec. In total, 14/83 (17%) persons belonged to a total of 8 clusters.

Conclusion: Our study has shown that HIV transmission among newly-diagnosed asylum seekers is occurring rapidly following arrival, and largely within specific ethno-cultural subgroups. This underscores the need for expedited screening and linkage to HIV care services to prevent onward transmission.
The Role of Myofibroblast in Infection and Inflammation

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Background: A growing body of evidence indicates that non-hematopoietic stromal cells of the intestine play active roles in maintenance of intestinal stem cells during homeostasis, inflammation, and infection. Previous work has demonstrated that intestinal infection triggers secretion of several proteins from the stroma, including R-spondins and EGF receptor ligands that are known drivers of epithelial regeneration upon injury. However, in certain susceptible mouse strains, deregulated expression of these stromal signals leads to hyperactivation of Wnt signaling, loss of intestinal epithelial homeostasis, and high levels of mortality. These findings indicate that proper regulation of regenerative signaling in stromal fibroblasts is a key component of the intestinal response to pathogens. Despite this understanding, little is known about upstream signaling pathways activated in stromal fibroblasts that trigger efficient repair of the gut epithelium in response to pathogens. Preliminary data has also revealed an equally important role of Yap and Taz (components of the Hippo pathway) in stromal cells of the gut. Indeed, we found that modulation of Yap and Taz activity in gut myofibroblasts in vivo severely disrupts intestinal barrier function and leads to deregulation of a panoply stromally derived secreted growth factors and extracellular matrix components.

Hypothesis: We hypothesize that Yap and Taz in stromal myofibroblasts may act as sensors of microbial infections and drive regenerative signalling in a paracrine fashion.

Specific aims:

Aim 1: Identify differentially expressed genes following treatment of immortalized human colonic fibroblasts cells (ie. CCD-18Co) and primary murine intestinal myofibroblasts to various bacterial products (eg. LPS) and common enteropathogens, like Citrobacter rodentium.

Aim 2: Determine whether the above transcriptional changes are regulated by Hippo signaling by modulating the activity of Yap and Taz in genetically modified intestinal fibroblasts.

Aim 3: Assess the impact of pathogens on the ability of fibroblasts to promote growth of the intestinal epithelium by treating intestinal organoids with conditioned media from infected and non-infected fibroblasts.

Impact: These studies will generate a greater understanding of the role of stromal cells in mediating host responses to infections agents in the gastro-intestinal tract. Enhancing tissue repair and barrier regeneration plays an important role in numerous infectious diseases and is also critical determinant of disease remission and recovery in patients with inflammatory bowel disease. By discovering the molecular pathways underlying intestinal regeneration, these studies will set the stage for developing new therapeutics mimicking tissue-reparative effects of invasive pathogens.
E-35 Role of Neutrophils in Cancer

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Background: Esophago-Gastric Adenocarcinoma (EGA) is the fastest rising malignancy in North America. EGA is associated with a poor five-year survival rate and the standard-of-care after diagnosis is limited to radiotherapy, chemotherapy (docetaxel, cisplatin, fluorouracil combination therapy; DCF), and surgery. Common to other cancers, EGAs develop chemoresistance which promotes disease progression. Recent studies have demonstrated the involvement of tumor-immune interactions in the development of chemoresistance. The majority of innate immune effector cells, the neutrophils, have been implicated in this interaction through the release of arginase, reactive oxygen species (ROS) and the production of neutrophil extracellular traps (NETs). However, other studies show that tumor-associated neutrophils (TANs) can directly inhibit tumor cell growth and metastasis through targeted cytotoxicity. Neutrophils’ ambiguous role in tumor progression is difficult to study due to their short lifespan. In this study, we will address neutrophils’ anti-tumoral behavior by developing co-cultures of neutrophils with EGA patient-derived organoids (PDOs) to model tumor microenvironment in vitro.

Method: Our group has generated over 60 EGA patient-derived organoids (PDOs) from both tumor and adjacent normal tissue. First, optimal growth medium for neutrophil survival will be identified using combinations of media used for primary cell growth. Second, neutrophils isolated from consented non-diseased and cancer patients will be co-cultured with PDOs from treatment naïve patients. Finally, the effect of neutrophils on PDO growth and response to docetaxel-based chemotherapy will be evaluated.

Conclusion: Developing a co-culture system that can be used to study the effect of neutrophils from good vs. poor responders to standard-of-care in combination with organoids from the same subgroups will guide future high throughout drug development assays. Assays that mimic the patient tumor microenvironment will allow for the identification of novel therapies that are likely to succeed in the clinic.
E-36  User interface redesign of the Opal patient portal app to allow informal caregivers to view patient data

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Introduction: Opal (opalmedapps.com) is an app that patients use to access their medical data and receive educational material and questionnaires related to their treatment. After some time, it became apparent that Opal's functionality should be extended to allow patients to share their medical data with their informal caregivers. In 2012, it was estimated that over a quarter (28%) of Canadians over the age of 15 had provided care for a family member or friend in the preceding year [Sinha, Maire. "Portrait of caregivers, 2012." (2013)]. This shows that many people could benefit from such an enhancement to the existing Opal app. For this purpose, an extension called “OpalCare” was created and is under development.

Objective: Our objective is to improve the Opal user interface to incorporate OpalCare and to make it more intuitive and in-line with user interface design standards.

Methods: We conducted user experience (UX) research using questionnaires to determine which features would benefit patients and caregivers the most. In parallel, we examined the current user interface and noted which features could be reorganized to improve user navigation. While referring to several popular user interface guidelines, we made low-fidelity prototypes (paper mockups) of suggested changes to quickly test and refine ideas. Currently, we are conducting UX testing with patient and caregiver pairs to evaluate and improve our prototypes.

Results: Originally, to view a certain patient’s medical records, the caregiver would need to select their patient’s profile on one page of the app and then navigate to another page which displayed the medical records. In the redesigned version, users change between patients’ profiles and view their medical records on the same page. We believe that this is more efficient for users who are caring for more than one person. Furthermore, we added more user feedback in the form of modals to let the user know whether an action was successful (e.g. confirmation of a change made) or when an action will be “destructive” (e.g. asking a user if they’re sure they want to exit a partially filled form).

Discussion: Our design was tested by having users perform tasks, such as sharing medical records with a caregiver, using our prototypes. The feedback was positive but we also found parts of design where there is room for improvement. We will continue to evaluate the design by conducting further UX testing with additional patient/caregiver pairs.
E-37 Investigating the function of Rab18 in regulating cytosolic lipid droplet storage in C. elegans

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Background: The excessive storage of neutral lipids in lipids droplets (LDs) is a consequence of excess dietary nutrient uptake and the primary cause of major metabolic disorders, including obesity, diabetes, and atherosclerosis. Recent proteomic studies investigating the profile of proteins associated with the monolayer surface of LDs to yield insights into the complex regulation of fat storage and mobilization have identified Rab18. Rab18, a small GTPase protein localized on the surface of LDs, plays a key role in several LD-related processes, including lipogenesis, lipolysis, and lipophagy. Although Rab18 has been previously associated with multiple functions, ranging from the negative regulation of secretion in neuroendocrine cells to mediating the apposition of LDs to the ER, its fundamental function in lipid metabolism remains disputed.

Methods and Results: To elucidate the function of Rab18 on cytosolic LDs, we attempted to identify effectors of Rab18 by a proximity-dependent labeling approach. A BioID screen for GTPase-deficient Rab18(Q67L) proximate and interacting proteins identified TBC1D5, a Rab7 GTPase-activating protein (GAP). The acknowledged function of Rab7 GTPase as a positive regulator of hepatocellular lipophagy led us to hypothesize that Rab18 could function in the recruitment of TBC1D5 to the surface of LDs to inhibit Rab7-mediated lipophagy. To validate this hypothesis and further understand the function of Rab18 in regulating LD storage at the organismal level, we performed a quantitative assessment of fat levels in RAB-18 knockout C. elegans under both fed and fasted conditions using Nile Red (NR) staining. C. elegans carrying the rab-18 (ok2020) deletion exhibited a significant reduction in NR fluorescence intensity compared to wildtype (N2) worms under both fed and fasted (6 hours) conditions (p<0.0001). We proceeded to investigate the effect of rbg-3 (TBC1D5) knockout on overall fat levels in C. elegans using NR and Oil Red O (ORO) staining. rbg-3 mutants exhibited significantly reduced NR fluorescence and ORO staining intensities compared to N2 worms under fed conditions (p<0.0001 for NR and p<0.001 for ORO).

Conclusions: Our findings are in accordance with the proposed hypothesis as the deletion of rab-18 or rbg-3 in C. elegans is associated with a significant reduction in overall fat content, which could be attributed to the loss of inhibition of Rab7 by its GAP RBG-3 (TBC1D5) and the subsequent activation of Rab7 mediated lipophagy. Further investigation into the function of Rab18 in lipophagy may contribute to our understanding of the conserved regulation of fat storage and metabolism.
The use of artificial intelligence in detecting sepsis in acute care patients and its clinical implications: A systematic review

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Purpose: The purpose of the present systematic review is to identify the effectiveness of AI technologies in detecting and/or predicting sepsis in adult acute care settings and the associated clinical implications.

Methods: The systematic review will be based off the guidelines provided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses for protocol (PRISMA-P) 2015 statement. A search of MEDLINE, EMBASE, SCOPUS, and CINAHL will be conducted through July 2019. The inclusion criteria for this systematic review will be any study that used artificial intelligence to detect sepsis, and the population of interest are adult patients hospitalized in acute care settings such as, critical care units, medical/surgical units, and/or emergency departments.

Preliminary findings: A randomised clinical trial reported that the machine learning-based severe sepsis prediction algorithm used in the study detected sepsis with higher sensitivity than the standard disease severity scoring systems that are currently used in hospital settings, such as the Systemic Inflammatory Response Syndrome criteria (SIRS) or the Sequential Organ Failure Assessment (SOFA). Furthermore, it was found that using the machine learning-based sepsis algorithm predictor resulted in significant reductions in length of stay and in-hospital mortality rates. In accordance with these results are the findings from a quality improvement study that also used machine learning-based sepsis prediction algorithms, which states that in-hospital mortality rates, length of stay, and sepsis-related readmissions rates all decreased. Further suggesting that machine learning-based sepsis prediction algorithms improves patient outcomes.

Conclusions: In order to improve and support the evolution of the healthcare system, this systematic review is needed to synthesize the existing knowledge on the effectiveness of these AI technologies and identify the current literature gaps. Based off the preliminary literature search, this systematic review will likely provide evidence of the beneficial use of artificial intelligence in detecting sepsis and how it improves patient outcomes. In addition, this systematic review will suggest a need to implement artificial intelligence technologies into acute care settings to detect sepsis, as it will aid in healthcare professions clinical decision-making.

Clinical relevance: Given the high mortality rate and economic burden of sepsis, it is essential that healthcare providers such as nurses and physicians, efficiently detect sepsis in time. Artificial intelligence technologies have shown to successfully aid in clinical decision-making and from the preliminary search findings, it is evident that artificial intelligence technologies are effective at detecting sepsis and thus can improve patient outcomes.
F-39 FHCanada Registry: our national registry for patients with familial hypercholesterolemia

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Familial hypercholesterolemia (FH) is the most frequent genetic lipoprotein disorder associated with premature CAD. The prevalence of FH in the general population has been recently revised to 1 in 250, so in Canada, the burden of disease is now estimated to be more than 143,000 patients, with less than 5% of patients diagnosed so far.

Objective: The goal of the FHCanada registry initiative was to create a registry of subjects with FH across Canada designed to identify subjects with FH and to improve health and healthcare delivery.

Methods: The registry was initiated in 2014 and regroups more than 200 basic researchers, clinicians specializing in lipidology, endocrinology, pediatric endocrinology, obesity and cardiology, clinical coordinators, and industry partners. Radiating from 19 main academic centers, the registry is being extended to various peripheral sites or communities (“hub and spoke” model). The database (iCAPTURE platform, James Hogg Research Centre at St-Paul’s Hospital, UBC, Vancouver) is using a uniform set of criteria and data entry, which includes clinical, biochemical and demographic information. Specimens (plasma/serum/DNA) are collected for local biobanking.

Results: More than 4,400 patients have been entered in the database so far. The FH Canada registry (www.fhcanada.net) has a strong knowledge translation component. Working together and using the data from the FHCanada database, the registry members have implemented evidence-based clinical practice guidelines for the adult and pediatric FH population and created educational resources and web-based applications to simplify FH diagnosis and treatment. These include a new simplified clinical definition of FH for the Canadian population and a new algorithm for the imputation of baseline LDL-C from LDL-C on lipid-lowering therapy, which were incorporated into the FHCanada database as subroutines as well as in a new application to ease the clinical diagnosis of FH, the “FH calculator” (www.circl.ubc.ca). Most recently, the first CLIA-certified molecular diagnostic test for FH has been designed and validated and this genetic test is now available to all physicians across the province and in the rest of Canada. The new genetic testing for FH is available to patients registering into FHCanada and will be useful for future research on the genetic aspects of the disease.

Conclusion: Through the creation of a Canada-wide network, the FHCanada registry is implementing useful tools, which will significantly improve the diagnosis of FH and care to patients with FH and reduce cardiovascular disease in this population at high risk.
Infants born with congenital heart disease (CHD) frequently present with brain dysmaturation and associated white matter (WM) injuries. However, it is still unclear whether these WM abnormalities impact WM metabolism over time. Therefore, the aim of this study is to further characterize the WM metabolic profile of young adults born with CHD. To do so, we used proton magnetic resonance spectroscopic imaging (H$_1$-MRS) to measure absolute metabolite concentrations in the centrum semi-ovale, a region commonly affected by WM injuries in neonates with CHD. Total N-acetyl-aspartate (N-acetyl-aspartate + N-acetyl-aspartyl-glutamate; tNAA), choline (glycerophosphocholine + phosphocholine; tCho), and creatine (creatine + phosphocreatine; tCr) were selected as these are well established markers of neuronal maturation, structural integrity, and energy level, respectively.

We acquired multi-voxel H$_1$-MRS data from the brains of 55 youths (16-24 years old) born with CHD and 49 healthy individuals using a 2D multivoxel PRESS sequence. For tissue characterization, we also acquired whole-brain high-resolution magnetization-prepared 3D T1-weighted gradient-echo sequence. H$_1$-MRS data were processed and analyzed using TARQUIN software, and T1-weighted MRI images were segmented into grey matter (GM), WM and cerebrospinal fluid (CSF) using the FSL FAST automatic segmentation tool. An in-house Python script was used to quantify the concentration of WM, GM, and CSF in each H$_1$-MRS voxel. Only voxels that had >80% of WM were selected for further analysis, and absolute metabolite concentration was obtained by applying a correction factor to convert metabolite signal intensity measurements into absolute units of concentration (mmol/L).

Preliminary results obtained in 16 CHD and 16 controls revealed that CHD had significantly lower tNAA (p < 0.03) and lower tCho (p <0.03) when compared to controls, while tCr was not significantly different. These preliminary results suggest youths with CHD have less neuronal maturity and signaling of cell membranes and will be further confirmed as we finalize the processing of our sample.
F-41 De novo and recurrent nonalcoholic steatohepatitis after liver transplantation: a prospective study employing cytokeratin 18 and transient elastography

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Background: Liver transplantation (LT) is a life-saving procedure that resolves complications of cirrhosis. However, the metabolic risk factors for nonalcoholic steatohepatitis (NASH) persist and potentially worsen in the post-transplant setting thereby increasing the risk for de novo or recurrent NASH. Due to the invasiveness of liver biopsy, prospective longitudinal data on the incidence of NASH following LT are scarce. We investigated incidence and predictors of NASH diagnosed by transient elastography (TE) with controlled attenuation parameter (CAP) and the biomarker of hepatocyte apoptosis cytokeratin 18 (CK-18) in LT recipients.

Methods: Consecutive LT recipients from a single centre were followed at 3 month intervals up to 1 year post-transplant. Fatty liver, significant liver fibrosis (stage 2 out of 4) and NASH were diagnosed as CAP>248 dB/m, TE measurement>8 kPa and CK-18>246 U/L, respectively. Predictors of de novo or recurrent NASH were determined using logistic regression analysis.

Results: 40 LT recipients (mean age 57+9 years, 72% men, BMI 25.6+4.6; 91% on immunosuppressive therapy with tacrolimus plus steroids and/or mycophenolate) were enrolled. The main indications to LT were NASH (26.5%), alcohol abuse (32.3%) and HCV (20.6%). At baseline (month 1 post-LT), there was a high prevalence of NASH, fatty liver and significant liver fibrosis likely due to residual inflammation affecting the results of the non-invasive tests adopted. Non-invasive diagnostic tests for liver disease showed high proportions of patients having NASH, fatty liver and significant liver fibrosis since the early period post-LT (see Table). Liver biopsy was available in 24% of patients and confirmed the non-invasive diagnosis of NASH, liver fibrosis stage and fatty liver in 87% of cases. By multivariable analysis, after adjusting for age and gender, independent predictors of de novo and recurrent NASH were higher BMI (odds ratio=1.30, 95% CI 1.02-1.67) and diabetes (odds ratio=5.15, 95% CI 1.08-24.5).

Conclusions: De novo and recurrent NASH is a frequent occurrence during the first year following LT. Early implementation of interventions targeting metabolic risk factors should be pursued.
Keloid scarring on earlobes is a condition that most commonly affects patients of African or Asian descent. Often disfiguring, this condition can have devastating psychosocial consequences. To date, no treatment modality has been proven optimal. Through a systematic review, we aimed to identify various treatment modalities used to treat earlobe keloid. An animal model experiment was conducted to determine the efficacy of botulin toxin type A for the treatment of keloid scars and to analyze the histopathologic changes that occur in an organized keloid scar following botulinum toxin type A injection as compared to steroid and saline injections. Medline, Pubmed, and Web of Science electronic databases were identified 520 articles. After critical review, 42 articles underwent a critical appraisal for the directness of evidence and risk of bias. Most commonly observed treatment modalities were excision, corticosteroid injection, and/or compression. Almost all earlobe keloids were caused by a piercing and found in patients of African descent.

In the animal study, keloid scars from earlobes of four patients were excised and implanted subcutaneously into 28 mice. Three small keloid tissue samples were implanted in each of the 28 mice. One week after implantation, each implant received one of three injections: botulinum toxin type A, saline, or steroid injection. The keloid tissue was extracted 3 weeks after implantation. Weight analysis, immunohistochemistry, and standard hematoxylin and eosin pathologic analysis were performed on each extracted tissue sample. Paired t-test analysis of pre-treatment and post-treatment tissue weights revealed a statistically significant difference between the treatment and control groups (p < 0.05). Analysis by a blinded pathologist confirmed fewer collagen bundles in the treatment group. Immunohistochemistry with Ki-67, a marker of cell proliferation, revealed significantly less staining in the treatment groups. Although various treatment modalities exist and are effective, no treatment seems to be more effective than another. Botulinum toxin type A could be an effective treatment for keloid scars.
F-43  Assessing the effects of TPD52 on cell growth inhibition by oleate.

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The metabolic syndrome affects close to 20\% of adult Canadians and is signified by having at least three of the following five criteria: High blood pressure (≥ 130/85 mm Hg, or receiving medication); High blood glucose levels (≥ 5.6 mmol/L, or receiving medication); High triglycerides (≥ 1.7 mmol/L, or receiving medication); Low HDL-Cholesterol (< 1.0 mmol/L in men or < 1.3 mmol/L in women) and; Large waist circumference (≥ 102 cm in men, 88 cm in women; ranges vary according to ethnicity (PMIDs 21911558; 30718342). This metabolic condition significantly increases the risk of developing chronic diseases including diabetes, cardiovascular disease, and non-alcoholic fatty liver disease (NAFLD) where the latter is frequently viewed as the hepatic expression of the metabolic syndrome. NAFLD affects about 25\% (Metrakos & Nilsson, 2018 PMID: PMID:28550272) of the general population and is characterized by having an accumulation of cytoplasmic lipid droplets (CLDs) in more than 5\% of hepatocytes with or without non-alcoholic steatohepatitis (NASH; i.e., hepatic inflammation). NASH is seen in about 20\% of NAFLD patients and signifies on-set of chronic liver disease progressing into fibrosis and cirrhosis with associated increases in mortality rates. Over time, this results in hepatic decompensation or hepatic cellular carcinoma (HCC). Our group is interested in hepatic components that promote NAFLD disease progression and have identified several novel CLD associated components through subcellular fractionation of human livers followed by quantitative liquid chromatography-tandem mass spectrometry. Of these, tumor protein D52 (TPD52), a calcium-regulated oncogene stands out as being relevant as this protein is overexpressed in several types of cancers, including HCC. We find that TPD52 correlates with cell proliferation as knock-down completely inhibits cell division and that expression of TPD52 overcomes CLD-induced cellular growth inhibition. Based on BioID, we link TPD52 to the lysosomal RAGULATOR complex that serves as a GEF for the mTORC1 complex. In this study, we monitored the growth of HEK293-TRex cells expressing a tetracycline-inducible TPD52 gene after addition of oleate. We observed that increased levels of oleic acid to induce CLD formation inhibits cellular proliferation and, that increased expression of TPD52 effectively overcomes such inhibition. We hypothesize that CLD-induced growth inhibition (as in NAFLD) is off-set by the increased expression of TPD52 to maintain cellular regeneration. Also, that such a scenario increases the risk of HCC.
F-44  Mechanisms of High-Fat Diet-Induced DNA Damage Repair in Prostate Cancer

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Epidemiological studies on prostate cancer (PCa) have identified diet, particularly diets rich in saturated fats, as a key factor that drives the progression of the disease. The current project investigates a potential mechanism that ties fatty diets to PCa progression. In vivo studies in MYC-driven murine models of PCa have demonstrated that high-fat diet (HFD; 60% fat – rich in saturated fat) increases the aggressiveness of PCa tumours, as demonstrated by an increase in tumour burden in HFD-fed mice, compared to mice fed a regular diet (CTD; 10% fat). Additionally, an increase in the levels of γH2A.X, a marker of DNA damage, was observed in tumours from HFD-fed mice before the appearance of an HFD-dependent phenotype, suggesting that HFD induces an accumulation of unrepaired double-stranded DNA breaks (DSBs). We will investigate the hypothesis that diet impacts the non-homologous end joining (NHEJ) and/or homologous recombination (HR) DNA damage repair (DDR) pathways, leading to an accumulation of DSBs and ultimately fuelling PCa progression. For this purpose, we will use two reporter systems to determine whether DSB repair favours either NHEJ or HR. Briefly, a single site-specific DSB is generated in an inactive green fluorescent protein (GFP) expression cassette containing a restriction site for I-SceI, a rare-cutting endonuclease. Upon repair via either NHEJ or HR, GFP activity is restored. These systems will allow us to monitor the effects that HFD-associated metabolites have on DSB repair. We will also clone I-SceI into a doxycycline-inducible vector, which will provide temporal control in vitro and make this system suitable for in vivo studies. We first assessed the basal levels of NHEJ and HR in our MYC-driven PCa cell model through transient transfection with reporter plasmids and the I-SceI vector. We have confirmed that NHEJ is the DNA repair pathway favoured by these cells. We will then expose cells that are stably transfected with the reporter system to murine plasma taken from animals fed either a CTD or an HFD, followed by doxycycline treatment to induce I-SceI-mediated DSBs. Altogether, this study will contribute to understanding how diet affects the DDR pathway in MYC-driven PCa. Further in vitro and in vivo studies using this inducible system will examine the effect of specific lipids on DDR in MYC-driven PCa cells, with the final goal of pinpointing which components of the diet play a role in deregulating the DDR pathway of PCa tumours.
F-45  Fuzzy -/- induces downregulation of key pathways involved in embryonic renal development

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**Introduction:** In the Western world, 0.5% of newborns display congenital anomalies of the kidney and urinary tract (CAKUT), such as small disorganized kidneys. In several cases, CAKUT is accompanied by progressive loss of renal functional, necessitating renal transplants. Dr. Torban’s laboratory recently generated transgenic mice, lacking a key Planar Cell Polarity effector gene, Fuzzy. These mutant mice display a CAKUT-like phenotype. At early stages of kidney development (Embryonic (E) day 14.5), Fuzzy mutant kidneys are significantly smaller. We found that renal hypoplasia is due to abnormal morphogenesis of the ureteric bud (UB), which gives rise to the collecting duct system. Several pathways are critical for UB branching: Glial cell-derived neutrophic factor (GDNF), Sonic Hedgehog (Shh) and Fibroblast Growth Factor/Fibroblast Growth Factor Receptor (Fgf/Fgfr). We performed transcriptional profiling of Fuzzy -/- vs wildtype kidneys to ascertain the expression of the genes known to control UB development.

**Methods:** We examined the gene expression in the wildtype and Fuzzy mutant kidneys microdissected from E14.5 embryos, followed by RNA extraction. Reverse transcription and quantitative Polymerase Chain Reaction (qPCR) were employed to analyze differences in gene expression levels. Student T-test was used for statistical analysis.

**Results:** Fuzzy -/- kidneys have significantly downregulated expression of the Shh and GDNF pathway genes. Expression of the genes in the Fgf/Fgfr pathway appears similar in the kidneys of both genotypes.

**Discussion:** These findings demonstrate that Fuzzy plays an important role in the regulation of Shh and GDNF pathways that are critical for kidney morphogenesis during embryonic development. In contrast, the absence of Fuzzy causes severe dysregulation of the expression of these genes. These findings bring us a step closer into understanding the pathogenesis of CAKUT.
Type 1 diabetes (T1D) is an autoimmune disease in which insulin-producing beta cells in the pancreas are destroyed. Diagnosis of T1D is often made automatically for any pediatric case that presents with hyperglycemia and ketosis, regardless of the results of autoantibody (aAb) or genetic autoimmunity marker testing. However, a number of monogenic forms of diabetes present with the same symptoms as T1D but can be treated with oral agents such as sulfonlureas instead of insulin injections. Onset is sometimes neonatal but, in most cases, it overlaps with that of T1D and is referred to as MODY (maturity-onset diabetes of the young), caused by mutations in any one of 14 genes, autosomal dominant in all cases. We propose that autosomal recessive forms of non-autoimmune, non-neonatal, non-syndromic diabetes exist, but have not been identified because of lack of suggestive family history – confined to diabetes in ¼ of the siblings, which is also common in polygenic T1D. The objective of this study is to test the hypothesis that a portion of cases diagnosed with T1D has non-autoimmune, monogenic autosomal recessive diabetes, and to identify the gene(s) mutated in this condition. We examined 2,436 nuclear families from the T1D Genetics Consortium (T1DGC), with two or more affected children. Entry criteria were young age of onset, uninterrupted insulin Rx, and at least one similarly affected sibling. In 39 families with unaffected parents, the affected children were negative for both aAb and high-risk HLA genetic markers, reducing the likelihood of autoimmune cause. Whole exome sequencing (WES) was used to examine DNA from one proband per family, and the WES data was filtered to select for protein-altering variants with an allele frequency < 1%. We designed PCR primers to flank the mutations that were found in the exome, to amplify these DNA regions of interest for Sanger sequencing. Sanger sequencing is used to confirm the exome finding in the proband, verify that the affected sibling has the same mutation(s), and confirm familial segregation of the mutation according to the genetic model. Preliminary results have confirmed a mutation in a known dominant gene, HNF1A, allowing us to remove this family from the search for novel genes. Mutations in a known gene (ZFP57) and a recessive candidate (INSR) were rejected for non-segregation in the family.
G-47  The pattern of claudin 3 and 8 at the boundary between the neural and non-neural ectoderm

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Introduction: Claudins belong to a protein family involved in a multi-protein complex in the apical membrane of epithelial cell layers: the tight junctions. These structures carry out important structural functions based on their capacity to homo/hetero-dimerize with other claudins, including the maintenance of epithelial integrity within the tissue, as well as the maintenance selective paracellular permeability. Furthermore, previous studies showed that the different members of the claudin family have unique patterns of expression that changes during embryogenesis. For instance, at HH10 in chick embryo, Cldn8 is expressed in the neural ectoderm (NE) and Cldn3 in the non-neural ectoderm (NNE). Throughout neurulation - a key step of embryonic development – the separation between NE and NNE requires the reshaping of the junctions at the contact point between these two tissues. Thus, we want to determine the dynamic changes of the Cldn3 and Cldn8 expression pattern during neural tube closure, particularly at the junction between NE and NNE.

Hypothesis: I hypothesise that the cells between the neural and non-neural ectoderm are expressing the two types of claudins at some point of the neurulation.

Material: For these studies, I am using immunofluorescence in whole mount embryos and histological sections. I target the Claudins 1, 3, 4, 8, and 14; I also use a ZO-1 antibody to label the tight junctions. For the slides, I used 3 different fixation agents: PFA, TCA and 6:3:1. For the embedding, I used both paraffin and OCT for the cryosection. Results: I observed a co-localisation of claudin 3 and 8 during the closure of the neural tube between neural and non-neural ectoderm. More interesting, the localisation of claudin 3 expressed in the top of neural ectoderm presents an apical expression in the cells composing the top of the neural tube, but seems to resorb with the setting up of the junctions between cells. Claudin 3 is more expressed around the point of closure once the two tissues are touching.

Discussion: I would like to understand the regulation of the expression of the mRNA of claudin 3 and 8 during the closing of the neural tube, in order to understand the evolution of their profile of expression in the neural tube during neurulation.
G-48 Smoking as a risk factor for spontaneous bone anchored hearing implant extrusion

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Background: The bone-anchored hearing implant (BAHI) was developed in the late 70s and since then has been used successfully to rehabilitate patients with conductive or mixed hearing loss who cannot benefit from traditional hearing aids. Successful osseointegration is a prerequisite for functional bone anchored hearing implants. Although not common, failure to achieve osseointegration or sudden loss of acquired osseointegration has been reported. Numerous studies have identified smoking as a risk factor for osteoporosis and bone fracture. Higher revision rates of orthopedic hip and knee replacements as well as dental implants in smokers compared to nonsmokers are known. There are limited reports examining the effect of smoking on bone anchored hearing implant survival (BAHI).

Methods and Results: We report a case of two BAHI extrusions occurring in a heavy smoker. The literature was reviewed to investigate the association between BAHI loss and smoking and the possible underlying mechanisms that may account for auditory osseointegrated implant loss and smoking. Our patient experienced delayed healing and increased pain around the abutment site despite an uneventful surgery. The implant extruded 2 days after sound processor coupling, and a second implant extruded 1 week after a revision surgery. Our literature review identified 2 other cases of implant loss in heavy smokers; one undergoing 6 surgeries. Smoking is thought to adversely affect hormones and enzymes involved in bone regulation, and to have an inhibitory effect on osteogenesis and on angiogenesis. At the cellular level, nicotine reduces the proliferation of red blood cells, macrophages, and fibroblasts and increases micro clot formation in blood vessels through increased platelet adhesiveness. In certain settings, smoking cessation just 4 weeks before surgery has been shown to significantly reduce post-operative complications.

Conclusions: Our case report and review of literature serve to demonstrate the risks associated with bone anchored hearing implant loss and smoking. These risks should be discussed with patients who are BAHI candidates and heavy smokers.
The removal of claudins in embryonic mouse submandibular gland explants results in abnormal branching morphogenesis

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Background: Development of the embryonic submandibular gland (eSMG) involves the process of branching morphogenesis: buds form and branch by clefting in which the basal membrane of the bud buckles. Defects in eSMG branching morphogenesis result in deficient salivary secretion and a medical condition known as xerostomia. Branching morphogenesis of tubular organs such as the SMG, lungs, and kidneys depends on communication between cells via junctional complexes. Claudins are integral proteins and the major backbone of tight junctions (TJ)—the most apical cell-cell junctional complex in epithelial cells that regulate paracellular transport of ions. In mammals, there are 24 members in the claudin family which are selectively expressed in different tissues. We have previously shown that the removal of specific claudins using the C-terminus of the Clostridium perfringens enterotoxin (C-CPE) resulted in decreased mouse embryonic kidney branching morphogenesis and lung lumen growth. We hypothesize that C-CPE treatment in the embryonic mouse SMG (emSMG) will impair branching morphogenesis.

Methods: Embryonic day (E)13.5 emSMG were grown in culture for 72 hours in the presence of 800μg/mL C-CPE and 560μg/mL GST. The salivary glands are paired structures therefore, one gland was cultured in GST, while the other was cultured in C-CPE to decrease any inter-embryo variability. The morphogenetic effect on lumen area growth, perimeter growth, cleft progression, and budding pattern was measured. Ongoing work includes confocal immunofluorescence microscopy to assess claudin protein expression in the emSMG and to determine if there is removal of claudins from tight junctions in C-CPE-treated emSMGs. Dextran experiment will also be performed on explants to determine whether paracellular transport of water is affected by the removal of claudins.

Results: Decreased lumen area growth, perimeter growth, and clefting among the C-CPE treated explants were observed when compared to GST-treated explants (P<0.05, n=7/group). Experiments are ongoing to increase the sample size of each group.

Conclusion: The findings demonstrate that submandibular gland explants grown in the presence of C-CPE exhibit a decrease in lumen area growth, lumen perimeter growth, and clefting. Further analysis should be done to determine if claudins are removed as a result of treatment with C-CPE.
G-50 Targeting the Misfolding-Associated Protein Secretion pathway to hinder the progression of Parkinson’s disease

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Parkinson’s disease (PD) is the second-most common age-related neurodegenerative disorder, for which there is currently no cure available. The cause of PD has been accredited to the development and spreading of alpha-synuclein (α-syn)-rich protein aggregates termed Lewy bodies which lead to neuronal death in the substantial nigra. Hence, α-syn aggregation and striatal dopamine deficiency are considered the main neuropathological hallmarks of PD. Recent studies suggest the possibility of prion-like neuron-to-neuron spreading of the pathogenic α-syn. The misfolding-associated protein secretion (MAPS) pathway has been recently discovered and shown to secrete misfolded cytosolic proteins including α-syn in cultured cells. We found that ER-embedded deubiquitylating enzyme USP19 which is the key regulator of the MAPS pathway is also expressed in the mouse brain. Thus, we want to test whether MAPS pathway contributes to the prion-like propagation of α-syn and is therefore detrimental to the PD-like brain. In my summer internship, I use a PD transgenic mouse model to test whether the absence of USP19 would influence the propagation and secretion of α-syn via the MAPS pathway in vivo and in primary neurons. To address this, I perform a wide range of techniques such as behavior tests, protein biochemistry, and immunofluorescence. The goal of this project is to provide a proof of principle for targeting the MASP pathway as a novel approach to the treatment of PD.
Diet-dependent immune infiltration in murine prostate cancer models

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Prostate cancer (PCa) is one of the most common types of malignant neoplasm and a major cause of mortality in males. Epidemiological evidence shows that environmental factors play a major role in PCa oncogenesis, among which diet is an important risk factor associated to PCa etiology, development and progression. High-fat diet (HFD) and obesity are related to higher PCa incidence and mortality and with the increasing daily intake of fat in modern society, it is of the uttermost importance to determine the underpinnings of this association. Immunosurveillance is a protective mechanism against foreign pathogens or cancerous cells in the body. With tumour progression, the immunosurveillance is compromised and shift to an immune evasion state. Previous study shows that high-fat intake contributes to PCa’s immune evasion, thus we hypothesize that HFD-induced obesity promotes PCa by dampening anti-tumour immune response.

C57BL/6 mice were divided at three weeks of age into two dietary groups. The HFD group was fed a diet consisting of 60% fat, while the control diet (CTD) group was fed a diet consisting of 10% fat. At 9-weeks of age, mice were injected subcutaneously into the flank with two murine-derived PCa cell lines driven by either Pten-loss (sKO) or the combined loss of Pten and Rb1(dKO). The endpoint of the study is set when tumour burden reaches an average of 400mm³ in one group. To determine the composition and the spatial localization of the tumour immune cells infiltrate, immunohistochemistry (IHC) will be performed. Markers such as CD4, CD8, CD68 and F4/80 will be used to stain respectively helper, cytotoxic T lymphocytes and macrophages. Combined to immunophenotyping data performed by fluorescence activated cell sorting (FACS) this study will describe how the immune infiltrate composition and localization can be influenced by tumour molecular drivers and the diet. Finally, it will provide a basis for further study centred on the impact of diet on the immune function and pave the way to novel therapeutic approaches in prostate cancer involving precision nutrition.

Keywords: Prostate Cancer – Immune system– Diet – Immunohistochemistry
G-52 Evaluation of Kidney and Blood Pressure Outcomes 11 Years Following Acute Kidney Injury in Critically Ill Children

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Background: Acute kidney injury (AKI) is common among children admitted to the pediatric intensive care unit (PICU). PICU-AKI is independently associated with poor hospital outcomes and increased health care utilization. In adults, AKI is a risk factor for chronic kidney disease (CKD) and hypertension (HTN). However, long-term renal outcomes associations with childhood AKI remain unclear.

Objectives: 1) Assess the prevalence of CKD, elevated blood pressure (BP) and HTN 11 years post-PICU admission and 2) Determine if AKI during PICU is associated with worsening outcomes from 6 to 11 years post-PICU.

Methods: This prospective cohort study recruited participants previously studied 6 years post-PICU admission to the Montreal Children’s Hospital. Children were evaluated 11±1.5 years post-PICU admission. Blood (for serum creatinine) and urine (for albumin-to-creatinine ratio [ACR]) were collected. Height, weight and BP were measured. The primary exposure was AKI during PICU (by Kidney Disease: Improving Global Outcomes definition). The main outcomes were CKD (estimated glomerular filtration rate [eGFR] <90 ml/min/1.73m² or albuminuria [ACR 3 mg/mmol]), elevated BP (BP 90th percentile or 120/80 mmHg in adults) and HTN (BP 95th percentile or 140/90 mmHg in adults).

Results: 100 patients were recruited (mean±SD age at PICU admission: 4.0±4.9 years-old; 58% male). While there was no significant difference between the CKD and HTN prevalence at 11-year vs. 6-year visit (CKD: 14% vs.18%; HTN: 3% vs.8%, p>0.05), there was a significantly lower proportion of participants with elevated BP at 11 vs. 6 years (17% vs. 21%; p<0.05). There was a significant decrease in mean±SD eGFR, systolic and diastolic BP percentile at 11-year vs. 6-year visit (eGFR: 124±29 vs.135±31 ml/min/1.73m²; systolic BP: 54±29 vs.62±25; diastolic BP: 43±20 vs. 53±24; all p<0.05). Yet, mean±SD urine ACR remained similar between 6-year (2.2±6.2 mg/mmol) and 11-year (1.5±2.0 mg/mmol) visits (p>0.05). PICU-AKI was not significantly associated with a mean±SD change in eGFR, ACR or BP percentiles from 6 to 11-year follow-up (eGFR change from 6 to 11-year: -16±19 in AKI vs. -10±31 in non-AKI; ACR change: 0.3±2.0 in AKI vs. -1.0±7.1 in non-AKI; systolic BP change: -10±32 in AKI vs. -10±33 in non-AKI; diastolic BP change: -11±17 in AKI vs. -11±25 in non-AKI; all p>0.05).

Conclusions: CKD, elevated BP and HTN were common 11 years post-PICU admission. However, having AKI in PICU did not predict CKD or BP worsening over time. Interventions are needed to reduce long-term cardiovascular risk in critically ill children. Risk factors for CKD, elevated BP and HTN worsening must be elucidated.