Summer Undergraduate Research Program (SURP)

AUGUST 11, 2021

RESEARCH DAY

9:00 am  Welcome
9:15 am  Keynote
10:30 am Podium Presentations
12:00 pm Lunch Break
1:00 pm  Poster Presentations
3:00 pm  Awards Ceremony

KEYNOTE SPEAKER:
DR. NAJMA AHMED
“Acumen to advocacy to action: the role of physicians and health advocates”

HTTPS://WWW.IMS.UTORONTO.CA/SUMMER-UNDERGRADUATE-RESEARCH-PROGRAM-SURP
2021 Summer Undergraduate RESEARCH DAY

Wednesday, August 11, 2021
9:00 am – 4:00 pm
Gather.town Virtual Platform

9:00 am  Welcome – Great Hall on gather.town virtual platform
Dr. Mingyao Liu, Director, Institute of Medical Science

Introduction of Keynote Speaker
Dr. Theodore Brown, Director, Summer Undergraduate Research Program (SURP)

9:15 am  Keynote Address
“Acumen to advocacy to action: the role of physicians and health advocates”
Dr. Najma Ahmed MD, PhD
Vice Chair of Education and Professor of Surgery, Department of Surgery, University of Toronto
Interim Surgeon-in-Chief, St. Michael’s Hospital

10:15 am  Break – Networking on the Patio

10:30 am  Student Oral Presentations – Great Hall, gather.town virtual platform

11:45 pm  Lunch Break & Networking – Patio, gather.town virtual platform

1:00 pm  Poster Presentations – Poster Rooms, gather.town virtual platform

3:00 pm  Award Presentations – Great Hall
Dr. Theodore Brown, Director, SURP; and Michelle Dubinsky, Program Coordinator

3:30 pm  Concluding Remarks
Dr. Mingyao Liu, Director, IMS

We thank our generous benefactors
Our sincere appreciation to the presenters of the 2021 SURP Seminar Series

Dr. Sylvie Lesuis, PhD, PDF in the Lab of Dr. Sheena Josselyn, SickKids
Dr. Jennifer Jones, Director, Cancer Rehabilitation and Survivorship Program, Butterfield/Drew Chair in Cancer Survivorship Research and Senior Scientist, Princess Margaret Cancer Centre, UHN
Dr. Mathieu Lemaire, MSc, MDCM, PhD, FRCP(C), FAAP, Assistant Professor, UofT; Staff Physician, SickKids
Dr. Chung-Wai Chow, MD, PhD, Clinician Scientist/Associate Professor, TGH and UofT
Dr. Muhammed Mamdani, PharmD MA, MPH, Vice President of Data Science & Advanced Analytics, Unity Health Toronto; Professor, UofT, Adjunct Senior Scientist at the Institute for Clinical Evaluative Sciences
Dr. Raphael Schneider, MD, PhD, FRCPC, Principal Investigator, Keenan Research Centre for Biomedical Science; Neurologist, St. Michael’s Hospital
Dr. Michael Corrin, PhD, Associate Professor, Teaching Stream, University of Toronto
Dr. Jody Jenkinson, Director, Biomedical Communications Program
Dr. Vasundara Venkateswaran, Graduate Coordinators of the IMS program
Dr. Mojgan Hodaie, MSc, MD, FRCSC, Clinician Scientist, Krembil Research Institute, TWH, UHN

Our sincere appreciation to the IMS Students, without whom the 2021 SURP Program would not be possible.

Laura Best, PhD Candidate
Jonathon Chio
Ergi Duli
Jesse Joynt
Nairy Khodabakhshian
Katie Lye
Isis So, MSc Candidate
Serena Peck
Jonathon Chio
Claire Wunker
Helen Yang
Isis So

Our sincere appreciation to the Judges and Co-Judges of the 2021 Research Day

Judges
Dr. Najma Ahmed
Dr. Samantha Anthony
Dr. Phyllis Billia
Dr. Edward Chow
Dr. Nomazulu Dlamin
Dr. Eyal Grunebaum
Dr. Magdy Hassouna
Dr. Adriana Ieraci
Dr. Hsiang-Yuan Lin
Dr. Gordon Moe
Dr. Raphael Schneider
Dr. Amit Singnurkar

Co-Judges
Ikran Ali
Julianne Baarbe
Melissa Chasse
Ergi Duli
Sonja Elsaid
Andreea Furdui
Javad Iqbal
Thivia Jegathesan
Sandy Lee
Rachel Liu
Haris Majeed
Lindsay Melhuish Beaupre
Daniel Merritt
Avinash Mukkala
Ernest Namdar
Neda Rashidiranbar
Brahmdeep Saini
Sherald Sanchez
Archita Srinath

Podium Presenters for SURP 2021

Alana Byeon (Supervisor: Dr. Mojgan Hodaie)
Yiyue (January) Jiang (Supervisor: Dr. Shreejoy Tripathy)
Tulip Marawi (Supervisor: Dr. Jennifer Jones)

Howard Schimmer (Supervisor: Dr. Milos Popovic)
Cassandra Stan (Supervisor: Dr. John Vincent)
Matthew Volpatti (Supervisor: Dr. Cindi Morshead)
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**Dantrolene Prevents Doxorubicin-Induced Cardiac Ryanodine Receptor Dyssynchrony**

**Background:** Ryanodine receptor 2 (RyR2) is important for cardiac calcium release from the sarcoplasmic reticulum. RyR2 activation triggers a spatio-temporally regulated calcium spark. Synchronous activation of RyR2 clusters creates a steeper slope and shorter systolic rise time in calcium transients. Doxorubicin (Dox) is a commonly used chemotherapy drug that can lead to dyssynchronous RyR2 activation and cardiomyopathy. We therefore sought to investigate the effects of RyR2 stabilizer dantrolene (Dan) on restoring normal RyR2 synchrony of calcium release in a murine model of doxorubicin-induced cardiomyopathy.

**Hypothesis:** We hypothesize that treatment with dantrolene will mitigate RyR2 dyssynchrony induced by doxorubicin.

**Methods:** 22 adult male C57BL/6 mice were randomly divided into four groups: (i) Control, (ii) Dox only (single intraperitoneal injection, 10 mg/kg on day 7), (iii) Dan only (10 mg/kg daily starting on day 0 through day 21), and (iv) Dan + Dox. Two weeks after Dox treatment, the hearts were harvested and perfused in a Langendorff setup. Calcium-sensitive dye Rhod-2AM and mechanical uncoupler Blebbistatin were infused. Each heart was electrically stimulated following a pace-and-pause protocol during optical mapping of the anterior ventricular wall. Dye fluorescence was recorded and analyzed using custom MATLAB codes. Time to rise (TTR), the time duration for Rhod-2AM fluorescence to rise from minimum (10%) to maximum (90%) in each heartbeat, was used to assess RyR2 synchrony.

**Results:** TTR was prolonged in the Dox group compared to control (11.6±1.3 ms in Dox group vs. 10.1±0.6 ms in control; at 14 Hz). Treatment with Dan prevented this prolongation (11.6±1.3 ms in Dox group vs. 9.8±0.6 ms in Dan+Dox group; at 14 Hz).

**Conclusion:** Our findings suggest that dantrolene is effective in mitigating RyR2 dyssynchrony induced by doxorubicin.
Supervisor: Dr. Istvan Mucsi

Exploring the information needs of African, Caribbean, and Black Community Members Regarding Living Donor Kidney Transplantation in Toronto, Ontario

**Background:** In Canada, patients with kidney failure from African, Caribbean, and Black (ACB) communities are 60-70% less likely to receive a living donor kidney transplant (LDKT) compared to white patients. Providing transplant-related information may improve equitable access to LDKT. However, little is known about information needs of ACB communities on LDKT in the Canadian context. Purpose: To better understand the information needs of ACB communities in Toronto, ON.

**Methods:** Purposive and snowball sampling were used to recruit self-identified ACB participants for in-person and virtual focus groups (FGs) (January-November 2020). In collaboration with community partners, an exploratory qualitative approach was used to guide discussions on racial and ethnic identity, medical experiences, and knowledge and perspectives on LDKT. FGs were audio recorded and transcribed verbatim. Thematic analysis directed the development of codes and themes. Analysis was informed by the tenets of Critical Race theory, which prioritizes racism as an important determinant of health.

**Results:** Of the 81 participants, 48% self-identified as Caribbean, 36% as North American Black/African, 4% as Central/West African, and 6% as North African. One major theme that emerged was a desire for tailored and trustworthy information on LDKT. Participants expressed mistrust in the health care system, rooted in historic and current experiences of racism, and this may impact willingness to engage with information on LDKT typically provided by medical institutions. This may be one reason why some participants described being unaware of the causes, consequences, and treatment options for kidney failure. Participants emphasized that future development of resources on LDKT would require collaboration with ACB communities to incorporate important cultural, preventive, and holistic elements e.g., nutrition preferences and religious beliefs. Conclusion: Future information on LDKT provided to ACB communities must be culturally tailored, trustworthy, and focused on preventive and holistic health.
Factors predicting delirium severity in older adults in the emergency department (ED)

**Background:** Older adults (>65 years) admitted to the ED with delirium are at higher risk of mortality, prolonged hospital stays, and adverse outcomes. Factors such as history of dementia contribute to worse delirium severity. There is evidence that the motor subtypes (hypoactive, hyperactive, mixed delirium) have different outcomes. Identifying factors that predict delirium severity classified by it’s subtypes could contribute to our understanding of delirium.

**Methods:** Secondary analysis from a multicenter study of a sample of older adults admitted to the ED was used. The mini-mental status exam (MMSE) and the Confusion Assessment Methods were used to assess delirium and it’s subtypes. 3 binary logistic regression models were used to estimate a polychotomous model: Model 1) hypoactive delirium vs. no delirium; 2) hyperactive vs. no delirium; and 3) hypoactive vs. hyperactive delirium.

**Results:** Sample included 1577 subjects (average age; 81 years, 49% female, 93.3% no delirium, 2.0% hypoactive, 4.7% hyperactive/mixed). Sex, age, education, presence of family members, ED length of stay and comorbidities were not statistically significant in any model. MMSE was a significant predictor in all models: Model 1 OR 1.27, 95% CI 1.2 to 1.3, Model 2 OR 1.2, 95% CI 1.2 to 1.3, and .0.91, 95% CI 0.84 to 0.98.

**Conclusion:** MMSE was predictive of delirium. Compared to hyperactive delirium, each increase in MMSE was associated with a 0.91 reduction in odds of having hypoactive delirium. Our hypothesis-generating analysis suggests that hypoactive delirium may be more common in those with more severe cognitive impairment compared to hyperactive delirium.
Investigating the frequency of renal monitoring in patients on HIV pre-exposure prophylaxis regimens containing tenofovir disoproxil fumarate

Background:

HIV pre-exposure prophylaxis (PrEP) has emerged as a new tool in HIV prevention. PrEP regimens containing tenofovir disoproxil fumarate (TDF) have been shown to reduce the risk of HIV infection by over 99%. TDF is generally well tolerated but carries a risk of nephrotoxicity and can result in tenofovir tubulopathy (<2%). Early detection and discontinuation can reverse kidney damage and thus routine renal monitoring is recommended. However, the optimal frequency for renal monitoring is not well-defined. Current Canadian PrEP guidelines recommend 3-monthly creatinine testing, but spuriously elevated measurements are common resulting in unnecessary testing, patient anxiety, increased use of physician time and even inappropriate discontinuation of PrEP. Therefore, less frequent monitoring can reduce these burdens if proved to be safe.

Objective:

We will investigate if extending the time between serial serum creatinine measurements from 3-monthly to 6-monthly results in lower detection of tenofovir tubulopathy.

Methods:

We performed a retrospective chart review of patients seeking PrEP between 1 January 2015 to 31 December 2020 at St. Michael’s Hospital in Toronto, Canada. Eligible patients who underwent standard 3-monthly serum creatinine measurements were assessed for instances of abnormal creatinine values, additional testing and tenofovir tubulopathy. To estimate the counterfactual outcomes in the comparison group, we will simulate 6-monthly renal measurements by only considering data from every other appointment in the same cohort of patients. For data analysis, descriptive and inferential statistics (t-test and simple linear regression) will be applied. Other outcomes assessed include eGFR trends and proportion of positive tubulopathy tests.
Using Chart Reviews to Evaluate a Continuing Medical Education (CME) Program

**Background** – Moore’s Expanded Outcomes Framework is a seven-level framework commonly used to assess the outcomes of continuing medical education (CME) programs. Levels 1 to 5 are provider-level outcomes (participation, satisfaction, knowledge, competence, and performance), while levels 6 and 7 are patient- and community-level outcomes. Chart reviews are one method to assess performance (level 5). ECHO Ontario Chronic Pain and Opioid Stewardship (“ECHO”) is a CME telementoring program that aims to increase capacity and access for primary care providers (PCPs) who manage patients with chronic pain. Each 2-hour weekly session includes a case presentation and a didactic lecture. This study uses chart reviews to evaluate ECHO’s impact on PCP performance and to discuss the feasibility of Moore’s framework.

**Methods** – Two ECHO staff traveled to PCP practices across Ontario to conduct chart reviews. A data extraction tool was developed and pilot-tested to capture changes in practice. Collected data included demographics, medical history, and pain and opioid management strategies (pharmacological and non-pharmacological), which mapped onto curricula taught in ECHO.

**Results** – 47 patient charts from 12 PCPs were included. 25 (53%) patients were male and the average age was 59 (± 14) years. 24 (51%) patients had two or more pain diagnoses at baseline, with musculoskeletal pain being the most prevalent at 81%. 26 (55%) patients had comorbid mental health conditions and 13 (28%) had sleep disorders. Trends in our results showed marginal, but non-significant, improvements in PCP performance after ECHO as indicated by increased use of pain management (ie, discussion of functional goals) and opioid management (ie, urine drug screens) strategies.

**Conclusions** – Conducting chart reviews was a challenging method to assess provider performance. Limitations included gathering individual patient-level consent, reliance on the quality of PCP chart documentation, and the time and cost of conducting a multi-site study in order to access patient chart information. Another challenge was the nature of collecting cross-sectional primary care data in this manner, when so much of care and management in primary care is incremental and longitudinal. Our study time period was not able to capture all previous relevant medical history. Future work to assess provider performance should include a qualitative component (in-depth interviews or focus groups) in order to complement the quantitative data and provide context for care and management decisions.
Examining the Association of Adolescent Medicine Care with Disease Outcomes of Patients with Childhood-Onset Systemic Lupus Erythematosus

**Background/Purpose:** Childhood-onset Systemic Lupus Erythematosus (cSLE) is a chronic, multi-organ, life-threatening disease with a median age of diagnosis between 11-12 years. In addition to the cSLE health burden, adolescent patients face typical psychosocial and development issues. cSLE patients may receive Adolescent Medicine (AM) specialist care to address additional health management challenges. Therefore, we examined the association of AM care with disease outcomes.

**Method:** We conducted a retrospective cohort study of cSLE patients (12-18 years old) receiving (n=104) vs. not receiving (n=57) AM care between July 2018 – July 2020 at the SickKids Hospital. Patient demographics and disease characteristics between patient groups were compared using appropriate statistical tests. Change in disease activity status and presence of disease damage were examined for association with AM care using univariate and multivariate logistic regression analysis.

**Results:** Table 1 shows patient characteristics. Patients receiving AM care were more likely to be of Black ethnicity, have higher disease activity, and glucocorticoid prescriptions. Several adolescent issues were addressed for cSLE patients in AM care; most prominent being mood. AM care status did not show statistically significant associations with change in disease activity (Odds Ratio:1.81) or presence of disease damage (Odds Ratio:0.48) in adjusted regression analyses. However, AM care provided psychoeducation for 57 (54%) of those seen.

**Conclusion:** No statistically significant association was established between AM care status and cSLE disease outcomes. However, many patients receiving AM care were provided psychosocial intervention, which may benefit their overall disease management. Future studies will explore the role of AM care in cSLE self-management.

| **Table 1. Characteristics of patients with cSLE by Adolescent Medicine care status** |
|-----------------------------------------------|-----------------|-----------------|-----------------|-----------------|
| **AM Care (n=104)** | **No AM Care (n=57)** | **p-value** |
| Black: N, (%) | 22, (21.1%) | 2, (3.5%) | 0.006 |
| Glucocorticoids: N, (%) | 87, (83.6%) | 36, (45.6%) | 0.006 |
| Baseline SLEDAI score: median, (IQR) | 4.0, (1.0-8.0) | 2.0, (0.0-4.0)* | 0.009 |
| SLEDAI: SLE Disease Activity Index, *: (n=56) |
White matter and deep grey matter structural variations in childhood moyamoya disease

**Background:** Moyamoya disease is a progressive steno-occlusive arteriopathy of the internal carotid arteries or its branches, increasing risk of stroke. More advanced disease is associated with lower cerebrovascular reactivity (CVR). In the adult Moyamoya population, negative CVR is associated with increased apparent diffusion coefficient (ADC) in normal-appearing white matter (WM), consistent with perfusion-related microstructural changes. The effects of negative CVR in children, however, are not well understood.

**Objective:** i) To determine whether regions of negative CVR exhibit changes in ADC in the normal-appearing WM of children with Moyamoya. ii) To determine the association between CVR and ADC with subcortical volumes.

**Hypotheses:** i) regions of negative CVR will exhibit elevated ADC and be negatively correlated with subcortical volumes. ii) CVR will be positively correlated with subcortical volumes.

**Methods:** Retrospective analysis of a consecutive cohort of children with moyamoya and no history of stroke, age-/sex-matched controls, diffusion-weighted, T1-weighted, and blood-oxygen-level-dependent functional magnetic resonance breath-hold CVR imaging will be conducted. Interhemispheric CVR and ADC parametric maps will be calculated for the right and left hemispheres on all subjects. All images will be co-registered and segmented into WM and 7 subcortical regions of interest (ROI) using an atlas-based approach. Positive and negative WM CVR voxels will also be used as ROIs. Mean ADC, CVR, and volumes will be calculated within each ROI and compared between groups, followed by regression analysis to determine associations amongst these variables within groups.

**Results:** Twelve children with moyamoya and no stroke (7 male, age mean: 12.9 years, median: 12.2, range: 6.5-17.1) and age/sex-matched healthy-controls were included.

**Conclusions:** We anticipate these results to provide a better understanding of how altered hemodynamics contribute to the more accelerated disease progression in children compared to adults. A future study exploring the relationships between hemodynamic profiles, micro- and macrostructural changes, and cognitive functioning may reveal a reliable symptomatic basis for monitoring disease progression.
Sex differences in patient journey to diagnosis, referral, and treatment of trigeminal neuralgia: implications for equitable care

Background: Trigeminal Neuralgia (TN) is a hyperactive facial nerve disorder that is more prevalent in females than males (a 2:1 ratio). TN literature has not specifically considered how sex differences may be associated with the clinical process to surgical treatment. This study sought to investigate sex differences in patient journey to diagnosis, referral, and treatment of TN and explore underlying factors that may contribute.

Methods: Classical TN patients (n = 100; 50 females, 50 males) who underwent Gamma Knife Radiosurgery as their first surgical procedure were retrospectively identified using a random number generator and evaluated through chart reviews at Toronto Western Hospital. Welch’s t-tests and Pearson correlations were conducted and visualized using Python libraries.

Results: Remarkable discrepancies between sexes in access to care were examined. Females had a significantly longer delay in referral (p < 0.01) than males, further impacting the total delay (p < 0.01) observed between sexes. Notably, this disparity is highlighted given that females report higher pain intensity (p < 0.05) at referral, but are referred later than males. Regardless of sex, medically intolerant patients had significantly shorter referral delay than tolerant patients (p < 0.001). When sex was considered, both tolerant and intolerant males received earlier referrals than females (p < 0.01), yet tolerant females encountered a significantly longer referral delay than intolerant females (p < 0.001).

Conclusion: Sex differences in the referral process to TN treatment were recognized, in which females endured a considerably longer journey than males. This disparity may be attributable to medication tolerance and pain intensity, highlighting the need for expedited treatment for females. Fortunately, patients at the Gamma Knife Clinic can expect to receive satisfactory care going forward. Overall, appropriate education and evaluation of TN should be implemented to reduce delays and improve equitable access to care across sexes.
The Impact of COVID-19 on the Provision of Pediatric Burn Care

On March 17\textsuperscript{th}, 2020, the Ontario government declared a state of emergency in response to the COVID-19 pandemic during which time people were instructed to stay at home. Given that 75 – 85\% of pediatric burns occur in the home, it is likely that the emergency orders had an impact on burn encounters at SickKids. Thus, the aim of this study is to investigate the impact of the COVID-19 pandemic on the provision of pediatric burn care at SickKids. In order to compare burn encounters before and after the application of the state of emergency, patient records were extracted and analyzed for two cohorts, pre-pandemic (01/04/2019 – 21/08/2019) and pandemic (01/04/2020 – 21/08/2020).

Preliminary analysis has shown a 23.8\% decrease in burn encounters at SickKids over the pandemic period, which may relate to hesitancy regarding hospital care during the early months of the pandemic. No significant changes were observed in the etiology of burns and age, gender or ethnicity of burn patients ($p > 0.05$). Interestingly, a significant increase in friction burns ($p < 0.05$) was observed which may be explained due to changes in home environments, such as use of treadmills and frequent household cleaning, or more children riding bikes as a result of the COVID-19 lockdowns. Overall, this study will help inform the provision of burn resources for potential future public health emergencies at the SickKids pediatric burn centre and will also help to identify areas for burn prevention initiatives in the community.
Nicholas Chan

Supervisor: Dr. Brian Feldman

Development of a Multimedia Consent Video to Recruit Pediatric Rheumatology Patients into a Research Study

Contributions are highlighted in: Nicholas C. Chan¹, Alisha Poppen, BSc¹, Adam Mosa, MSc, MD¹, Clarissa Tsai, MLT¹, Rebecca Slack, Brian M. Feldman MD, MSc¹–³, Y. Ingrid Goh, PhD¹,²

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Background: Generally, patients joining research studies must provide informed consent. Although written informed consent is the most common practice, studies have shown that it may not be the most effective nor preferred method to ensure reader understanding. Limited pediatric studies have suggested that multimedia consent offers a standardized alternative that improves patients’ understanding and satisfaction for both clinical and research informed consent. To date, no investigations have examined the use of multimedia consent in pediatric rheumatology.

Objective: The purpose of this project was to develop an animated multimedia consent video to use for a future pediatric rheumatology study comparing multimedia and traditional consent processes.

Methods: An initial script and set of still images were developed. Feedback was obtained on the script and illustrations in an iterative fashion, informing their revisions. Input was sought on the order of presentation. Still images were animated using VideoScribe 3.7.3622 and Adobe Illustrator 2020. Audio was recorded using QuickTime Player 10.4. Feedback was also obtained on the video, which informed additional edits.

Results: Guidance was provided by numerous stakeholders which included physicians, allied health, family advisory council members, students, volunteers and an REB manager. Examples of revisions included language simplification and the inclusion of culturally diverse characters. After 10 iterations, we created an accessible multimedia consent video which was 6min 48s in length.

Conclusion: The development of an animated multimedia consent video requires input from multiple stakeholders, contributing unique perspectives that aid in translating complex concepts into a short and understandable video.

Appendix: The multimedia consent video - https://sickkidsca-my.sharepoint.com/:v:/r/personal/ingrid_goh_sickkids_ca/Documents/00-SPARRK/NicholasChan/MVP/PR-COIN%20July%205th%202021.mp4?csf=1&web=1&e=Wfb5VT
Worldwide Trends and Characteristics of Randomized Clinical Trials in Cardiac Surgery

**Background:** Randomized clinical trials (RCTs) are key to deriving high-quality evidence. To date, the characteristics of cardiac surgical RCTs remain unclear.

**Purpose:** To characterize trends and effects of location, intervention, sponsor type, trial phase, and patient age on trial status of cardiac surgery RCTs over time.

**Methods:** ClinicalTrials.gov was queried using Python 3.9 from 1988 to present. Descriptive statistics were performed using $\chi^2$, Fisher’s exact, and Mann-Whitney tests. Trends over time were depicted graphically.

**Results** After excluding observational studies and studies with incomplete dates, 2,822 trials were included. 50.5% of trials were completed, 39.7% in progress, and 9.8% prematurely stopped. Trial registration increased linearly from 6 in 2000 to 234 in 2019 (+3900%) and decreased to 201 in 2020 (-14.1%) (Figure 1). Trial completion increased from 0 in 2000 to 23 in 2016 and decreased linearly to 16 in 2020 (-30.4%). The most common study phases were phase 3 or 4 (26.1%). 11.5% and 5.7% of trials were sponsored by industry and federal agencies, respectively. The most common interventions were drugs (39.7%), procedures (24.4%), and devices (21.6%). Most (77.1%) trials enrolled adult and elderly patients. Trials originated from Europe (42.8%), North America (34.1%), and Asia (20.2%), whereas 6.1% originated from multiple continents.

**Conclusions** The initiation of trials increased from 1988 to 2019 but decreased throughout the COVID-19 pandemic. Trial completion increased until 2016 but decreased after, warranting further investigation.

![Figure 1. Number of randomized clinical trials initiated by year stratified by current (July 2021) trial status as presented in ClinicalTrials.gov.](image)
Trajectories of Depressive Symptoms in Systemic Lupus Erythematosus Over Time

Depression is one of the most frequently observed psychiatric disorders in patients with systemic lupus erythematosus (SLE), a chronic autoimmune disease with significant neuropsychiatric manifestations. Despite a prevalence of 35.0%, optimal management of the mood disorder is limited by the incomplete understanding of its trajectory. With fluctuating periods of exacerbation and remission of SLE, potentially accompanying shifts in depressive symptoms need to be accounted for in depression treatment and management. Our aims were to: 1) determine longitudinal trajectories of depressive symptoms in patients with SLE and 2) identify baseline factors that predict a patient’s trajectory of depression, particularly those linked to persistent and/or decreasing symptoms. Longitudinal data on 763 adults with SLE followed over 7 years from a single center were analyzed. Depressive symptoms were assessed annually in years 2-7 using the validated screening measure, the Center for Epidemiologic Studies Depression Scale (CESD). Group-based joint trajectory modeling was used to model latent classes. Using only members with latent class posterior probability > 0.8, univariable and multivariable analyses were employed to examine baseline factors associated with latent class memberships. Four distinct trajectories were identified: 1) lowest CESD scores (no depression, 36%), 2) moderate CESD scores (no depression, 32%), 3) high CESD scores (depression, 22%), and 4) highest CESD scores (depression, 10%). Increases in age and education levels were found to be protective variables in regression analysis while decreases in SF-36 physical functioning score, SF-36 bodily pain score, and income were associated with higher CESD scores and depression. These trajectories and associated baseline factors may help in identifying individuals with SLE who are at the greatest risk of developing persistent depressive symptoms, improving overall treatment outcomes.
Breast, Cervical and Colorectal Cancer Screening Rates among Canadians with and without Self-Reported Visual Impairment

**Background:** Adherence to cancer screening guidelines can lead to early detection and reduced mortality. Individuals with visual impairment (VI) may participate in cancer screening less than those without VI due to barriers in reading, driving, and ambulating.

**Purpose:** To compare rates of government-funded screening for breast, cervical and colorectal cancer in Canadians with and without VI, and examine associated sociodemographic factors.

**Methods:** Self-reported data on vision, mammography, pap smear, fecal occult blood test participation, and sociodemographics were analyzed from respondents to the Canadian Community Health Survey 2013/2014 and 2017/2018.

**Results:** Canadians with VI had lower participation rates in breast (53.0% vs. 67.0%) and cervical (53.8% vs. 76.2%) cancer screening at recommended time intervals compared to those without VI in 2013/2014. Colorectal cancer screening rates at the recommended interval were similar amongst those with and without VI (25.7% vs. 24.7%), and were comparable by sex. Having a family physician did not close the gap. Lower household income was associated with lower screening rates for all cancers examined. The 2017/2018 data similarly revealed a lower mammography screening rate (61.9% vs. 69.4%) and a comparable colorectal cancer screening rate (40.7% vs. 38.0%) in Canadians with and without VI. Cervical cancer screening information was unavailable in 2017/2018.

**Conclusions:** Canadians with self-reported VI have lower breast and cervical cancer screening rates than those without. Having a family physician did not impact this difference. Policy-makers, organizations and clinicians should understand the unique barriers faced by individuals with VI, and facilitate their adherence to appropriate screening practices.
Investigating the location of action of low-intensity focused ultrasound (LIFUS) within the human motor cortex

Low-intensity focused ultrasound (LIFUS) is an emerging but powerful method for non-invasive neuromodulation, representing a potential novel treatment for various neurologic and psychiatric disorders. This project aims to characterize the location of action of LIFUS within the primary motor cortex (M1), using a combined transcranial magnetic stimulation (TMS)-LIFUS approach. The direction of TMS current flow affects the level of M1 activation: anterior-posterior (AP)-directed currents activate superficial cortical layers, posterior-anterior (PA)-directed currents activate deep cortical layers, and lateral-medial (LM)-directed currents activate subcortical layers. We hypothesize that LIFUS sonication at a depth of 30 mm will reduce M1 excitability with AP-directed current, and sonication at a depth of 50 mm will reduce M1 excitability with LM-directed current. 3 right-handed, healthy subjects participated in this pilot study. TMS was delivered in the AP, PA, and LM current direction. For each orientation, three blocks of 20 TMS-LIFUS stimuli were delivered in random order (30 mm, 50 mm, or sham sonication). TMS was delivered 10 ms before the end of sonication to the left M1 hotspot of the first dorsal interosseous (FDI) muscle. Surface electromyogram (EMG) was recorded from the right FDI muscle. LIFUS sonication at both 30 mm and 50 mm depths reduced TMS-elicited M1 activity in 2 out of 3 subjects with LM- and PA-directed current and increased M1 activity in 2 out of 3 subjects with AP-directed current. These preliminary findings suggest that LIFUS sonication at 30 mm and 50 mm depths may affect multiple cortical layers simultaneously. Data collection is ongoing.
Development of an Electronic Pediatric PROMs Delivery Platform: Voxide

**Background:** Patient-reported outcome measures (PROMs) effectively capture patients’ perspectives and engage patients meaningfully.

**Purpose:** This research program aims to improve health outcomes for pediatric solid organ transplant patients by systematically implementing PROMs into clinical practice. Prior research phases included a systematic review (Phase 1), key stakeholder interviews (Phase 2), and a consensus workshop (Phase 3). The aim of this study (Phase 4) was to design an electronic PROM platform – Voxide – to collect and integrate PROM data into clinical workflow.

**Methods:** End-users, including patients and healthcare providers (HCPs), were central to the design process as a ‘user-centric’ approach guided Voxide development. Iterative testing sessions involved participants completing 1) tasks on Voxide wireframes to evaluate effectiveness and efficiency, and 2) the Microsoft Desirability Toolkit (patients), a system usability scale (HCPs), and a semi-structured interview to assess satisfaction and gather feedback.

**Results:** Twelve heart, kidney, liver, or lung transplant recipients aged 10-17 years and 16 members of their healthcare teams participated. Rapid, iterative, and sequential testing rounds demonstrated improved effectiveness as the proportion of successfully completed tasks increased from 74% to 85%. Efficiency improved as time-to-task decreased from 23.2 to 15.8 seconds. Patients described Voxide positively and remarked “[Voxide] makes you feel like you’re welcome in the hospital”. HCPs highlighted that Voxide is intuitive and enabled “a more patient-centered model of care”.

**Conclusions:** Findings demonstrate positive objective and subjective outcomes to guide Voxide development to drive clinical adoption and success. Future research includes usability testing and an implementation effectiveness evaluation trial.
The relationship between cleaning product exposure and respiratory and skin symptoms among healthcare workers in a hospital setting: a systematic review and meta-analysis

Abundant studies have reported an increase in respiratory symptoms in workers exposed to cleaning or disinfecting agents; however, the studies have mainly focused on occupational cleaners, and the relationship between respiratory and skin symptoms remains unclear. Healthcare workers often perform many cleaning and disinfecting activities and may be vulnerable to respiratory and skin symptoms caused by exposure to cleaning and disinfecting agents. The purpose of our study was to conduct a systematic review and meta-analysis of the available literature to quantify the risk of respiratory symptoms in healthcare workers exposed to cleaning or disinfecting agents and to identify risks of skin symptoms in those studies. We searched MEDLINE, EMBASE, CDSR, CENTRAL, and CINAHL databases. Studies that evaluated the association of respiratory outcomes in relation to occupational cleaning exposures in healthcare workers were included, and among those studies skin outcomes were also evaluated. The NHLBI quality assessment tools were used to assess the quality of the included studies. We retrieved a total of 1,663 articles. After applying our inclusion criteria, 27 studies were selected to be included in the systematic review. A meta-analysis of eight studies evaluating the association between occupational cleaning exposures and asthma demonstrated a 44% increased risk in exposed healthcare workers (meta-relative risk (RR)=1.44; 95% CI 1.23 to 1.70). The risk of asthma increased when workers were exposed to bleach (meta-RR=1.41; 95% CI 1.02 to 1.94). Only one study investigated the relationship between respiratory and skin symptoms. Studies that investigated skin symptoms as a secondary outcome reported mixed results. Preventative practices for healthcare workers exposed to occupational cleaning or disinfecting agents are necessary to reduce resultant respiratory symptoms. Further research regarding skin symptoms and the relationship between respiratory and skin symptoms in exposed healthcare workers is highly recommended. Trial registration number: CRD42020137804.
“It wasn’t that great”: Challenges in Patient-Provider Communication after Kidney Transplant – a Qualitative Study

Background: Kidney transplantation is a life-altering treatment, but many patients experience physical or psychosocial symptoms post-transplant. Managing these symptoms requires effective communication between patients and healthcare providers (HCP). Yet, research shows that there are challenges in this area, and suboptimal communication may contribute to suboptimal assessment and management of symptoms. Purpose: In this qualitative analysis, we explore patient experiences in communicating with their HCP after a kidney transplant. Methods: We used Qualitative Description methodology to understand the quality of communication between recipients and HCP post-transplant. We utilized purposive sampling (flyers and snowball recruitment, June2020-June2021). Semi-structured, in-depth, individual interviews were conducted over Microsoft Teams platform by a research associate and two students in Toronto. The interviews were audio-recorded and transcribed verbatim. Content analysis directed the iterative development of codes and categories. Results: Eight transplant recipients (5 males, ages 36-75, 1-15 years post-transplant) described a range of experiences, from regular contact with HCP to little perceived opportunity to communicate between appointments. Compared to pre-transplant care, communication was less frequent and recipients described feeling isolated and unsure how to seek information and support. They relied on searching for information online, visiting family doctors or the emergency room. Some connected with HCP over the phone, but this was not always timely nor efficient. Even those who described regular access to HCP felt that the focus was more on the physical and less on the psychosocial aspects of their health. Conclusion: Communication challenges between kidney transplant recipients and HCP contribute to feelings of isolation and difficulties navigating post-transplant life. Regular monitoring of patient-reported biopsychosocial outcomes, and tailoring communication to individual preferences may improve individualized care.
Interventions designed to increase the uptake of lung cancer screening and implications for priority populations: A scoping study

**Background:** Lung cancer screening using low-dose CT (LDCT) can detect early-stage tumours potentially leading to reduced mortality due to lung cancer. However, various social determinants of health impact the accessibility of healthcare services, which can lead to inequities in access to lung cancer screening and lung cancer related health outcomes. Populations that experience barriers in accessing lung cancer screening due to economic, structural, and geographic barriers as well as stigma associated with smoking are identified as priority populations. While interventions have been designed to increase accessibility of lung cancer screening, little is known about the positive/negative and intended/unintended impacts on priority populations. This knowledge can inform the design of equitable lung cancer screening services.

**Purpose:** To create an overview of existing lung cancer screening interventions designed to increase uptake of lung cancer screening and to identify their potential impacts on priority populations.

**Methods:** We are using the methodological framework of Arksey and O’Malley to guide the scoping review with identifying the research question, identifying relevant studies, selection of studies, data extraction, reporting the results and knowledge translation for patient and public involvement. We utilized various research databases (OVID Medline, Embase, the Cochrane Library, CINAHL and Scopus) to conduct comprehensive searches regarding lung cancer screening uptake interventions.

**Results:** Our search yielded 2681 articles, of which 16 met our inclusion criteria; 16 grey literature articles were also included. Selected articles were dated from January 2000 to January 2020 and were conducted primarily in the USA, Europe, and Canada. We used the ‘Patient Centered Access to Healthcare’ conceptual framework by Khanassov et al 2016 and identified four interrelated themes which describe accessibility of lung cancer screening interventions for priority populations: (i) limited outreach to priority populations, (ii) limited tailoring of interventions to target priority populations based on cultural and social practices (iii) few methods to reduce financial, practical, and time barriers to care and (iv) little fit between intervention design and underlying social patterns of disparities.

**Conclusion:** This scoping review has identified potential implementation gaps and health inequities in lung cancer screening interventions which will inform the development of lung cancer screening practices to prevent the further widening of health inequities that burden priority populations.
The Effect of Transcranial Ultrasound on Interhemispheric Inhibition

Interhemispheric inhibition (IHI) refers to a neural mechanism in which activation of one hemisphere of the brain inhibits the opposite hemisphere, presumably via callosal projection neurons. At the motor cortex (M1), IHI can be measured using conditioning-test transcranial magnetic stimulation (TMS). Low intensity focused ultrasound stimulation is a promising non-invasive transcranial brain stimulation (NTBS) technique for therapeutic development, with increased focality and depth in comparison to other NTBS. Previously, we showed that transcranial ultrasound (TUS) inhibits TMS-evoked MEPs in the ipsilateral M1. Thus, we hypothesized that TUS will also inhibit TMS-evoked IHI. Twenty healthy right-handed subjects were recruited. Stimulation was applied to the first dorsal interosseous (FDI) muscle hotspots in M1 and surface electromyography was recorded at FDIs. In the first experiment, active or sham TUS was given for 500ms with a TMS test stimulus (TS) at 490ms over right M1. In the second experiment, active or sham TUS was given for 500ms with TMS conditioning stimulus (CS) at 490ms over right M1, and TS at 500ms (short IHI (SIHI)) or 530ms (long IHI (LIHI)) over left M1. Baseline activity was measured by 500ms sham TUS and TS at 500ms. The last experiment replicated the second, but without TMS-CS. Results showed that TUS application reduced MEPs in the right M1 and TMS-evoked LIHI, but not SIHI. In addition, TUS without TMS-CS did not affect TMS-TS. These findings suggested that TUS may have an effect on the neural circuit underlying LIHI, but not SIHI or tonic IHI.
The Link Between HIV Antiretroviral Therapy and Ultrasonic Vocalizations

Introduction: HIV antiretroviral therapy (ART) use in pregnancy has significantly reduced the vertical transmission rate of HIV. However, despite the recognized benefits of this therapy, many studies indicate developmental delays in children who are HIV exposed but uninfected (CHEU). An increase in Autism Spectrum disorder (ASD) has been noted in CHEUs and a potential link to mitochondrial dysfunction has been suggested. As the number of CHEUs continue to increase worldwide, it becomes increasingly important to understand the long-term effects of being exposed to HIV and ART in utero and to identify the safest regimens to use in pregnancy for optimal maternal and infant health. We have established a mouse model to help investigate the long-term effects of in utero ART exposure. Previous work in the lab has identified developmental delays in pups exposed to different ART regimens. In this study we examine pup ultrasonic vocalizations, a potential indicator of ASD-like behavior.

Hypothesis: We hypothesize that ART in pregnancy alters the in-utero environment and thereby alters neurocognitive development in pups leading to an increased prevalence of ASD-like behavior in CHEUs.

Methods: Throughout pregnancy, female mice were orally gavaged with atazanavir/ritonavir (ATV/r - a protease inhibitors) administered with either abacavir/lamivudine (ATV/r/ABC/3TC), or tenofovir/emtricitabine (ATV/r/TDF/FTC), or water as control. Treatment was terminated at day of birth. Pup ultrasonic vocalizations (USV) were recorded daily starting on postnatal day 3-day 10. Pups were separated from their mother and placed alone in a new cage. USV were recorded for 5 minutes. Call parameters were quantified for frequency, amplitude, wave type, and duration.

Results: Results for this study are still being quantified. Scoring of pup calls was done using Avisoft Bioacoustics Software and call types were quantified based on call shape, duration, amplitude, and frequency range. Calls are observed for differences in-between treatment groups, in comparison with the control, and for sex differences. USV analysis was used as different call types and parameters are used in different social situations and are useful for behavioral phenotyping of neurodevelopmental disorders such as ASD.

Conclusion: As ART use and access increases, policy reform and further clinical research is needed to ensure the safety of ART for neonates. If atypical USV parameters are observed in the ART exposed pups it may indicate the different lexicons and communication abnormalities often seen in children with ASD and should encourage further investigation into which specific brain structures ART potentially impacts.
Assessing the Association Between Pain and Health-Related Quality of Life in Kidney Transplant Patients using the PROMIS Pain Summary Score

**Background:** Chronic pain is highly prevalent in patients with end-stage kidney disease (ESKD) and is associated with poorer health related quality of life (HRQOL). **Purpose:** We assess the association between pain and HRQOL in kidney transplant recipients (KTR). **Methods:** A cross-sectional convenience sample of adult KTRs were recruited in Toronto, ON. Patients completed PROMIS (Patient Reported Outcome Measurement Information System) tools and other validated questionnaires on an electronic data capture system on tablet computers. Only patients who completed our exposure and outcome questionnaires were included in this secondary analysis. Pain was assessed using PROMIS pain summary score (PROMIS PSS), that is calculated using the PROMIS pain interference z-score and a weighted PROMIS pain intensity score. The primary HRQOL outcome was the EQ-5D (European Quality of Life 5-Dimension) score. The SF-12 PCS (Short Form 12 Physical Component Score) and SF-12 MCS (Short Form 12 Mental Component Score) were secondary outcomes. Descriptive statistics, correlation analysis, and quantile regression adjusted for potential confounders were used to analyze the data. Multiple Imputation by chained equation was used to address missing values. **Results:** Of the 312 participants (mean (SD) age=51(16)), 58% were male and 59% were white. Mean (SD) PSS and EQ-5D score was 49.5 (9.5) and 0.84 (0.15) respectively. The PSS correlated strongly and negatively with EQ-5D score (rho=-0.66; p<0.001). For the secondary outcomes, PSS had a strong negative correlation with SF-12 PCS (rho=-0.66; rho<0.001) and a weak negative correlation with SF-12 MCS (rho=-0.38; p=0.003). In a multivariable quantile regression, the association between PSS and EQ-5D score (B=-0.007; p<0.001; 95%CI: -0.008, -0.006), SF-12 PCS (B=-0.725; p<0.001; 95%CI: -0.828,-0.621) and SF-12 MCS (B=-0.179; p=0.003; 95% CI: -0.295,-0.635) remained significant after adjusting for socio-demographic and clinical co-variables, including depressive symptoms. **Conclusion:** We demonstrated that pain as measured using the PROMIS Pain Summary Score is independently associated with HRQOL among kidney transplant recipients.
A Pharmacogenetic Review of Opioid Pain Management and Opioid Replacement Therapy

Opioid abuse in North America is a public health crisis with a huge economic burden and immeasurable societal costs. It is vital to understand the underlying mechanisms of opioid addiction and uncover subtle risk factors which predispose patients to it. Genetic variation may be useful in explaining large interindividual differences observed in response to opioid use. This review aims to synthesize current pharmacogenetic research on major opioids such as morphine, oxycodone and fentanyl. Genes involved in opioid action, such as OPRM1, are the most widely studied in pharmacogenetic literature, but fail to adequately explain the variation between individuals. Polymorphism in genes related to opioid metabolism, specifically those encoding liver enzymes from the cytochrome P450 family, affects the speed and efficacy of opioid metabolism, significantly impacting opioid exposure. The major treatment of opioid addiction is Opioid Replacement Therapy (ORT), which replaces the use of an abused opioid with a steady dose of slower acting opioids. However, as opioid class drugs are used in these treatments, genetic variation could be significantly altering their safety and efficacy. It may be possible to improve the efficacy of ORT by tailoring treatment around individual patient’s genotypes at key sites. By combining the genetic information from multiple relevant loci, it is hypothesized that the relative efficacies and risks of methadone and buprenorphine can be accurately compared on a case-by-case basis to aid in the selection of an ORT treatment plan.
Assessment of cold allodynia in mice with neuropathic pain using the thermal place preference test

**Background:** Chronic neuropathic pain is a debilitating morbidity of neural injury. Yet, due to the inherent weaknesses of behavioural tests used in animal drug trials, new treatment development remains limited. The acetone drop test is the current gold standard used to assess a prevalent neuropathic symptom: cold allodynia, i.e., increased sensitivity to normally innocuous low-temperature stimuli, in neuropathic mice. However, it is limited by its inability to detect a range of temperatures. Alternatively, the thermal place preference test (TPPT) can assess cold allodynia across different temperatures; however, it has not been well established to evaluate neuropathic pain.

**Hypothesis:** The TPPT can distinguish cold sensitivity between neuropathic and naïve mice.

**Methods:** The spared nerve injury (SNI) model, the lesion of two terminal branches of the sciatic nerve, was performed on mice to induce neuropathic pain. The TPPT design monitored the time mice spent on a metal plate whose temperature ranged from 10-25°C compared with an adjacent reference plate fixed at 25°C. Protocols varied by the time spent per temperature. Total time spent per temperature was compared across SNI and naïve mice.

**Results:** I found that SNI mice spent less time on the aversive cold plate than naïve mice, most notably at 10 and 12.5°C. Detailed statistical analysis is ongoing.

**Conclusion:** At this point in my method development, my TPPT protocols can distinguish cold alldynia in SNI mice from naïve mice, possibly enabling us to develop an improved test to record the effects of new treatments on cold sensation in neuropathic pain.
Fatima Faruq

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Additional Authors: Danguecan, Hendrikx, Neufeld, Quilter, Korczak, Schachter, Cost, Couture, Dominguez, Ng, Levy, Hiraki

Cross-Sectional Analysis of Physical Activity and Dietary Habits in Children with Systemic Lupus Erythematosus

Background

Childhood-onset systemic lupus erythematosus (cSLE) is an autoimmune disease characterized by multi-organ involvement. Diet and physical activity have been linked to overall health and well-being in children. Poor physical activity and dietary habits in adults with autoimmune diseases have been associated with higher disease activity, but little work has been done in children with cSLE.

Objectives

We aimed to describe physical activity and dietary habits in patients with cSLE in reference to Canada’s nutrition and 24-Hour Movement guidelines for children and youth.

Methods

This cross-sectional study utilized data from 55 patients with cSLE (8-18 years old) recruited from the Lupus Clinic at The Hospital for Sick Children (2017-2019). Diet and exercise habits were measured by the Heart Niagara Inc. Healthy Lifestyles Assessment, a self-report questionnaire.

Results

The median patient age was 15 years (IQR 14, 16), 86% (47/55) were female, and median disease duration was 3.9 years (IQR 2.5, 6.4). With respect to Canadian guidelines: only 7% (4/55) of cSLE patients met weekly moderate to vigorous physical activity; 24% (14/55) met strength-related activity; 92% exceeded recommended 2 hour-limit on recreational screen time/day, with mean 5 hrs (SD=3.2). Regarding diet, only 41.3% (26/55) met fish-intake guidelines, and 50% did not meet breakfast recommendation of 7 days/week, with mean 4 days skipped/week (SD=2).

Conclusions

In this cohort of cSLE patients, the majority did not meet Canadian nutrition and exercise guidelines. Next steps include comparison of exercise and dietary habits in cSLE patients to normative peers, and examination of the relationship of these habits with cSLE disease activity.
An Investigation of Notch Homolog 2 N-terminal-like (NOTCH2NL) as a Possible Biomarker of Psoriatic Arthritis Susceptibility in Patients with Psoriasis

Introduction/Background: Psoriasis (PsC) is a chronic inflammatory skin condition characterized by excessive proliferation of keratinocytes. About one third of PsC patients develop psoriatic arthritis (PsA), an immune mediated inflammatory musculoskeletal condition. Early detection and treatment of PsA is imperative to prevent severe joint damage which impacts quality of life and mortality outcome. Thus, there is a need to identify early biomarkers for PsA pathogenesis. Preliminary analysis of differentially expressed genes in PsC and PsA patients found notch homolog 2 N-terminal-like (NOTCH2NL) to be up-regulated in PsA patients. NOTCH2NL plays significant roles in inflammation and osteoclastogenesis. However, its implication in PsA is not fully understood, therefore its usefulness as a biomarker requires further validation.

Purpose: The purpose of this study was to evaluate whether NOTCH2NL could be used as a biomarker for PsA susceptibility in PsC patients.

Methods: Serum NOTCH2NL levels were measured in 36 PsA (<2 years disease duration), 36 PsC (>10 years disease duration) and 36 healthy controls using commercially available ELISA kits. All patients were matched on age and sex; PsA and PsC patients were also matched on psoriasis duration. Next, serum NOTCH2NL levels were also measured in 20 PsC patients who did not develop PsA (non-converters), 20 PsC patients before they developed PsA (pre-converters) and the same 20 patients after they developed PsA (post-converters). All samples were run in duplicates. Mann-Whitney U test and Wilcoxon matched-pairs signed rank test were used for statistical analysis.

Results: Serum NOTCH2NL levels were elevated in the PsA group compared to both the PsC and control groups. Further, NOTCH2NL levels were higher in non-converters compared to both pre-converters and post-converters. Pre-converters had elevated NOTCH2NL compared to their matched post-converters. Despite these trends, there were no statistically significant differences among the groups (p>0.05).

Conclusion: The lack of statistical significance may be attributed to the small sample size. Despite this lack of significance, the elevated NOTCH2NL in PsA patients and decreased NOTCH2NL levels in post-converters, demonstrate the potential use of NOTCH2NL as a biomarker. This study should be repeated with a larger sample size to increase the statistical power of the study.
The Will to Live- II Study

Introduction: The Will to Live-II (WTL-II) is a longitudinal, mixed-methods study run by the Department of Supportive Care at Princess Margaret Cancer Centre. This study aims to determine the prevalence, trajectories, and predictors of medical assistance in dying (MAiD) requests in patients with advanced cancer.

Hypothesis: The desire for death, physical suffering, depression, hopelessness, death anxiety, and a greater desire to maintain a sense of personal control in patients will predict subsequent requests for MAiD. It is also hypothesized that patients receiving psychosocial and palliative care services are less likely to request MAiD.

Methods: This study aims to recruit 1000 cancer patients and 1000 primary caregivers. All participants will be asked to complete questionnaire packages at baseline and biannually for the duration of the study or until they choose to withdraw. Aspects such as one’s psychosocial and physical wellbeing, quality of life, will to live, access to supportive care services, and attitudes towards MAiD will be assessed using various quantitative measures. 30 participants will be selected to participate in 30-60 min. qualitative interviews.

Results: 1248 patients were prescreened. 79.6% of the patients were female and over 50% were recruited from Gynecology. 297 patients were eligible and identified to the physicians as prospective participants. The physicians confirmed the eligibility of 108 of the patients and 38 of them agreed to participate in the study. 15 baseline questionnaires were returned.

Conclusion: Prescreening and recruitment procedures will continue. Analyses of the questionnaire data and conduction of the qualitative interviews will proceed shortly.
Greater than the sum of its parts: a comparison of palliative care interventions for patients with heart failure and dementia

**Background:** Palliative care improves quality of life (QOL) in patients with heart failure (HF) but not dementia. The reasons for this difference are unknown and may be related to differences in PC interventions.

**Purpose:** To compare PC interventions between HF and dementia patients with a specific focus on the presence of an interdisciplinary care team (IDT) that addresses the holistic needs of patients with serious illness.

**Methods:** All trials of PC interventions for patients with heart failure or dementia were included from a recent systematic review and updated literature search. Narrative synthesis and descriptive analysis were performed using the National Consensus Project framework to evaluate PC across 8 domains. An IDT was defined as the presence of physician and/or nurse and at least one other healthcare professional.

**Results:** In total, 16 trials were included in the analysis (HF: 11 trials, n=4,475 patients; dementia: 5 trials, n=1,167 patients; mean age 75 years, 48% female). An IDT was present in 4 (36%) trials of HF patients and in 1 (20%) trial of dementia patients (16% difference, p<0.05). Trials with an IDT addressed an average of 6/8 PC domains, and 3.5/8 domains were addressed in trials without an IDT.

**Conclusions:** The inclusion of an interdisciplinary care team was more common among trials of patients with HF and addressed significantly more palliative care domains than in trials of patients with dementia. Prior observed differences in QOL outcomes may be related to variation in the breadth of palliative care interventions, including the presence of an interdisciplinary care team.
Classic Trigeminal Neuralgia is Associated with Hippocampus Diffusivity Abnormalities

**Introduction:** Trigeminal Neuralgia (TN) is a chronic neuropathic pain disorder associated with paroxysmal shocks of unilateral orofacial pain. TN patients report altered memory and cognition, functions attributed to the hippocampus. We previously demonstrated TN patients have reduced hippocampal subfield volume compared to healthy controls. To examine microstructural subregion abnormalities that may precede volumetric reductions, Diffusion Weighted Imaging (DWI) of TN hippocampi was utilized.

**Hypothesis:** We hypothesize that in addition to volumetric abnormalities, TN patients will demonstrate selective subregional microstructural abnormalities, as detected by Diffusion Tensor Imaging.

**Methods:** T1-weighted (T1w) anatomical images of 18 age and sex matched surgically naïve TN patients were segmented via FreeSurfer. Advanced Normalization Tools were utilized to co-register T1w and DWI scans and transform hippocampal subregions; head, body and tail segmentations into DWI space. FSL was utilized to extract diffusivity metrics; fractional anisotropy (FA), radial, axonal and mean diffusivities (RD, AD, MD) from hippocampal subregions.

**Results:** TN patients had markedly lower FA in bilateral whole hippocampi, particularly on the contralateral side of pain ($p_{\text{contra}}<0.001$, $p_{\text{ipsi}}=0.014$). TN patients had significantly reduced FA in bilateral hippocampal heads, ($p_{\text{contra}}<0.001$, $p_{\text{ipsi}}=0.049$). Female TN patients had significantly reduced FA in ipsilateral whole hippocampus ($p=0.014$), contralateral whole hippocampus ($p=0.005$), and contralateral hippocampal head ($p=0.0014$). No significant differences were determined for AD, RD and MD values.

**Conclusion:** We demonstrated a subregion specific reduction of FA in the hippocampi of TN patients, indicating a selective reduction in microstructural integrity. These results may implicate the hippocampus as a neuroanatomical correlate for abnormal TN patient cognition.
Characterizing microglial cells in patch-seq datasets

Patch-seq is an emerging method for sampling transcriptomic, electrophysiological, and morphological data from the same neurons. During the procedure, a patch pipette forms a tight seal with the outer membrane of a neuron. This prompts surrounding microglia, the resident immune cells of the brain, to migrate towards the pipette and ‘attack’ it. We hypothesize activated microglia are inadvertently sampled in subsequent RNA sequencing during patch-seq. Therefore, we aim to confirm the presence of microglia in transcriptomic data produced by patch-seq experiments and describe their functional profile.

This project leverages publicly available patch-seq transcriptomic data from the Allen Institute for Brain Science (AIBS). Using R packages such as Seurat and markerGeneProfile, we found a cluster of cells with high expression of microglial genes in both the human and mouse datasets. To understand the functional state of these putative microglia, we performed differential expression analysis between cells with the most and least microglial-like transcriptional profiles. We also compared our putative microglia to microglia identified in single-cell RNAseq datasets from the AIBS. The resultant gene lists were compared to a paper about microglial subtypes (Olah et al., Alzheimer's & Dementia, 2020) using hypergeometric tests and gene set enrichment analysis (GSEA). We further annotated for biological functions using the gene ontology (GO).

Our results show that the microglial cells in patch-seq datasets display a range of transcriptomics profiles, including disease associated and homeostatic programs. The cells are also enriched for immune responses and neuronal activity, suggesting that there is a mixture of different subtypes of microglia. We believe that that patch-seq datasets are indeed populated with microglial cells that inhabit various functional states.
The Role of Ninj1 in Hepatocellular Death Following Inflammatory and Ischemic Insult

**Background:** Nerve injury-induced protein 1 (Ninj1) is a widely expressed adhesion molecule whose loss of expression significantly decreases plasma membrane rupture of macrophages after pyroptotic cell death. In the context of liver transplant, ischemia-and-inflammation-induced cell lysis in the donated liver primes the recipient’s immune system for an anti-transplant response. Ninj1 therefore represents a potential target to decrease cell lysis and improve liver transplant outcomes.

**Purpose:** To examine how Ninj1 levels in hepatocytes are affected by ischemia, inflammation, and an ischemic-inflammatory combination.

**Methods:** HepG2 cells were exposed to 2µg/mL lipopolysaccharide (LPS) or 0.1ng/mL interleukin 6 (IL-6) for 8 hours to induce inflammation. 8 hour hypoxia was induced chemically using 12.5µM carbonyl cyanide-3-chlorophenylhydrazone (CCCP) or physically using a hypoxic (2.7% O2) incubator. Gene expression was measured with quantitative PCR and protein levels were measured with Western Blot.

**Results:** Inflammation of HepG2 cells with LPS or IL-6 decreased NINJ1 mRNA expression, as did CCCP-induced hypoxia and CCCP + LPS. Only CCCP + IL-6 increased NINJ1 expression. It is anticipated that changes in protein levels will show similar results.

**Conclusions:** This data suggests that inflammation or hypoxia alone do not increase Ninj1 levels in hepatocytes, unlike in macrophages. Since hypoxia combined with IL-6-induced inflammation increases Ninj1 levels, Ninj1 may be relevant in the context of liver transplants. Future experiments will examine levels of cell lysis to examine links between Ninj1 levels and cell lysis rates.
Sex Specific Gene Expression in The Periaqueductal Gray after Pain Priming

Background and Introduction: Chronic pain affects millions of people worldwide and leads to widespread disability, but its causes are still not well understood and there are few effective treatments. One possible cause of chronic pain is pain priming, in which pain-inducing interventions during early life result in lasting changes to adult pain sensation and response. The periaqueductal gray (PAG) is a brain region critical to the control of pain, acting through pathways including the descending pain pathway. The mechanisms and effects of chronic pain are also sexually dimorphic, and sex differences may interact with pain priming in ways yet unknown.

Purpose: This study investigated the effect of sex and injury status on gene expression in the PAG of Norway rats using the R software, identifying significantly differentially expressed genes (DEGs) under each condition (pain-primed_M vs naïve_M, pain-primed_F vs naïve_F, naïve_M vs naïve_F, and pain-primed_M vs pain-primed_F).

Methods: Several R packages were used to analyze DEGs in each of the four group comparisons mentioned above.

Results: No genes were uniformly upregulated or downregulated across samples in the comparisons by sex, suggesting minimal sex differences within the naïve and pain-primed states separately. Nevertheless, many DEGs were found in the comparisons by injury status (naïve male vs pain-primed male and naïve female vs pain-primed female).

Conclusions: The two sexes appear to arrive at the pain-primed state through different molecular pathways. These results demonstrate the complexity of sex differences in chronic pain and highlight the need for further research in this area.
Obstructive sleep apnea is associated with markers of cerebral small vessel disease in a dose-dependent manner: A systematic review and meta-analysis

Introduction: Cerebral small vessel disease (CSVD) affects perforating arterioles, capillaries and venules of the brain and is a major contributor to dementia, stroke and incident death (1). CSVD manifests on neuroimaging as white matter hyperintensities (WMH), lacunes, or cerebral microbleeds (CMBs) (2). Based on shared physiological pathways of disrupted cellular repair and metabolic waste clearance, it is posited that sleep disorders such as obstructive sleep apnea (OSA) may be closely linked with CSVD.

Purpose: To perform a systematic review/meta-analysis that will examine whether OSA severity is related to an increased likelihood of exhibiting CSVD.

Methods: This study has been registered and performed in accordance with PRISMA standards. We conducted a search of Medline, Embase and Cochrane for studies reporting the association between OSA and CSVD. We performed parallel meta-analyses of adjusted odds ratios (OR) and unadjusted ORs using event rates. The prevalence of CSVD was compared between groups with no OSA (apnea-hypopnea index <5), mild OSA (AHI 5-14), moderate-severe OSA (AHI ≥15) and severe OSA (AHI ≥30).

Results: A total of 32 observational studies were included in our analyses. Of these, 24 studies reported effect sizes for WMHs, 4 for CMBs, and 11 for lacunes. Upon combining the unadjusted ORs, we found greater OSA severity to be significantly associated with a greater likelihood of WMHs. Compared to those without OSA, the odds of possessing WMHs were 1.73 [95% CI 0.85; 3.55] for patients with mild OSA, 3.86 [2.73; 5.45] in moderate-severe OSA, and 4.31 [1.94; 9.60] in severe OSA (Table 1). We also discovered potential, albeit nonsignificant, dose response between OSA severity and lacunes and CMBs. These findings were supported by similar trends observed by meta-analyzing adjusted ORs.

Conclusions: This systematic review/meta-analysis revealed a dose-response relationship that has not been previously reported between OSA severity and WMHs. Our findings lend credence to ongoing studies that posit that treating OSA may result in stabilization or reduction in the burden of CSVD (3).

Table 1. Association between OSA severity and neuroimaging markers of CSVD using unadjusted ORs

<table>
<thead>
<tr>
<th></th>
<th>AHI &lt;5 vs. 5-15</th>
<th>AHI &lt;5 vs. ≥15</th>
<th>AHI &lt;5 vs. ≥30</th>
<th>AHI &lt;5 vs. ≥5</th>
<th>AHI &lt;5 vs. ≥15</th>
</tr>
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<tbody>
<tr>
<td>WMH</td>
<td>1.73 [0.85; 3.55]</td>
<td>3.86 [2.73; 5.45]</td>
<td>4.31 [1.94; 9.60]</td>
<td>2.76 [1.73; 4.41]</td>
<td>3.19 [2.07; 4.91]</td>
</tr>
<tr>
<td>Lacunes</td>
<td>0.83 [0.46; 1.49]</td>
<td>2.40 [0.83; 6.96]</td>
<td>3.37 [0.59; 19.14]</td>
<td>1.39 [0.60; 3.21]</td>
<td>2.96 [1.47; 5.97]</td>
</tr>
<tr>
<td>CMB</td>
<td>0.52 [0.12; 2.24]</td>
<td>4.06 [0.26; 62.79]</td>
<td>Not combined</td>
<td>2.41 [0.08; 69.39]</td>
<td>2.60 [0.09; 73.59]</td>
</tr>
</tbody>
</table>

* p < 0.05. Effect sizes are presented as OR [95% CI].

The YinYang Balance of Healing: A Qualitative Study of Barriers to Living Kidney Donor Transplantation in Chinese-Canadians

Background: Chinese-Canadians have increased risk of kidney failure and are substantially less likely to receive living donor kidney transplant (LDKT), compared to Whites. Research suggests that potentially conflicting health beliefs, values, and practices between Western and Traditional Chinese Medicine (TCM) may contribute to barriers limiting willingness of Chinese-Canadians to consider LDKT.

Purpose: In this analysis we use qualitative data from a mixed-methods study seeking to understand barriers to LDKT among Chinese-Canadians.

Methods: Purposive and snowball sampling were used to recruit Chinese-Canadian patients and community partners to participate in semi-structured interviews conducted over the phone/MS Teams in the participant’s preferred language(s) (English, Mandarin/Cantonese). Open-ended questions were asked about transplant-related knowledge, attitudes towards kidney transplantation, and cultural factors. Audio was recorded, transcribed, and analyzed via thematic analysis using inductive and deductive development of codes, categories, and themes.

Results: Six participants (1 LDKT recipient, 1 live-kidney donor, 4 participants without kidney failure experience; 3 females) were interviewed and described cultural and contextual factors influencing their views and experiences of LDKT. Conflicting values between TCM and Western medicine is emerging as a major theme. Identified sub-themes include importance of integrity of both kidneys for overall well-being of the individual. This may induce concerns about donating one kidney, in spite of its very low risk from a Western, physiological point of view. Participants also expressed preference for non-invasive traditional herbal remedies. Our interviews suggest that experience with kidney disease/failure and with the Canadian healthcare system may increase acceptance of Western medical practices over TCM.

Conclusion: In this preliminary analysis we found that TCM values and practices (e.g. emphasis on balance, use of herbal remedies) may influence attitudes of Chinese-Canadians towards LDKT and live kidney donation. Culturally tailored, comprehensive information about kidney disease and kidney failure treatment options may improve access to LDKT for Chinese-Canadians.
Death Anxiety in Advanced Cancer Receiving Palliative Care: A Preliminary Analysis of Prevalence and Correlation

Background: Death anxiety, which refers to distress about dying and death, may be common in individuals with advanced cancer but has received relatively little attention. Relief of such distress is an important goal of cancer palliative care, but the extent to which death anxiety is present in patients receiving palliative care has not previously been reported.

Purpose: To identify the prevalence and correlates of death anxiety in individuals with advanced cancer attending a palliative care outpatient clinic at a comprehensive cancer center.

Methods: 84 outpatients with advanced cancer were recruited between March 2020 and July 2021 from the Princess Margaret Cancer Centre Outpatient Palliative Care Clinic, as part of a larger study. The Distress about Dying and Death Scale (DADDS) and other self-report measures of distress were administered to the study participants. Descriptive statistics and preliminary correlation analyses were performed on the data collected.

Results: The mean level of death anxiety on the DADSS was 25.2 (±15.4), which falls in the range of at least moderate severity (DADDS≥25); 52.3% of participants had DADDS scores above this cut-off. Severe death anxiety (DADDS≥47) was reported by 7.1% of the sample. Death anxiety was correlated with other measures of psychological distress (p<.000 to p<.049) but not with demographic factors.

Conclusion: Death anxiety is common in patients with advanced cancer who are receiving palliative care and is associated with other manifestations of psychological distress. Death anxiety and the effectiveness of therapeutic interventions to relieve this phenomenon in this population deserve further investigation.
Training Machine Learning Models Can Predict Outcomes of Stem Cell Implantation

Spinal cord injury causes partial to complete loss of function below site of trauma. While neural stem cell implantation is a treatment method that shows promise, its unpredictability and cost make it difficult to be applied into practice directly. Hence, it would be insightful and efficient to make predictions based off of data accumulated over previous experiments. Machine learning algorithms can help to create a model that makes a prediction on the outcome of a stem cell implantation. Using the previously collected database, a random forest classifier model has been trained to predict the behaviour improvement of the subjects and a multilayer perceptron (MLP) neural network model has been trained to predict the proportions of neural stem cell differentiation. During the training, coefficient of determination was used to score how well the model fit the data, and the model was trained with various setups in order to search for the ideal setup. It was determined that for MLP model, the model was best fit when trained over 500 epochs with input properties: distance covered by injection, whether if injection was at epicentre or in rostral/caudal direction off of injury site, the species that is receiving the treatment, days after treatment which outcome was observed, number of cells injected, and depth at which the cells were injected. At ideal setup, average coefficient of determination was $0.46 \pm 0.07$, but it recorded a score of over 0.70. Machine learning algorithms can be used to provide insight into a treatment before it is given.
Clinical Implications of Frailty in Hospitalized Patients with Pulmonary Arterial Hypertension

**Background/Rationale:** Frailty is a biological syndrome characterized by decreased physiological reserve and is associated with increased morbidity and mortality in chronic lung disease. However, the role of frailty in pulmonary arterial hypertension (PAH) has not been well described, which may have significant implications on resource utilization and prognosis. We aimed to evaluate the prevalence of frailty in hospitalized PAH patients and assess its impact on hospital length of stay (LOS), resource utilization, and discharge disposition.

**Methods:** Retrospective cohort study of consecutive PAH patients admitted to Toronto General Hospital (January 2010 – December 2016) with PAH due to decompensated heart failure, infection, or hemodynamic instability. Frailty was defined as a cumulative index score of $\geq 0.25$, which was comprised of comorbidities, laboratory investigations and functional parameters based on accepted convention. Patient disease characteristics, hospital LOS, resource utilization (i.e. multidisciplinary consultations), and discharge disposition were compared between frail and non-frail patients using t-tests and chi-squared tests.

**Results:** Frailty was observed in 40 of 62 (64.5%) PAH patients. The median age was 62 IQR [50-76] years, 79% were female, and had a mean BMI of $27 \pm 6 \text{ kg/m}^2$, with no difference in age, sex or BMI between frail and non-frail PAH patients. There was a significant difference in hospital LOS between frail and non-frail patients (10 days IQR [6-15] vs 6 IQR [3-11], p = 0.02). Frail patients were more likely to need inpatient consultation from social work (94% vs 6%, p = 0.005) and palliative care (30% vs 5%, p = 0.023), but not from physiotherapy or occupational therapy services (40% vs 19%, p=0.15). There were no differences in critical care unit admissions (18% for both groups, p =1.0), but there was a trend for higher hospital mortality in frail patients (23% vs 5%, p= 0.08).

**Conclusion:** Frailty is associated with a longer hospital LOS and a greater likelihood of needing interdisciplinary support during hospitalization. Future studies will need to explore the prognostic implications of frailty beyond hospitalization.
Incidence of Long COVID post COVID-19 in CONCOR-Donor participants

**Background:** Coronavirus disease (COVID-19), caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) lead to a global pandemic. Most infected individuals never require hospitalization, and recover quickly, however, many have persistent COVID-19 symptoms/long-COVID. Incidence and clinical characteristics in those developing long-COVID remain unknown.

**Hypothesis:** Persistent COVID-19 symptoms will differ by sex and age.

**Objective:** Determine incidence of long-COVID in CONvalescent Plasma for COVID-19 Research (CONCOR)-Donor study participants.

**Methods:** This national observational longitudinal study, is recruiting participants over 17 years old, with a positive PCR test for COVID-19/positive household contact. Participation includes questionnaires and biological samples collected at enrollment, 6, and 12-months. Long-COVID is defined as symptoms persisting >30 days after infection. All statistical analysis is conducted using RStudio.

**Results:** Among 778 participants, 69% are female, mean age 42 (± 14) years old, 81% Caucasian, 66% from Ontario, 20% from Alberta, and 14% from other Canadian provinces. Approximately 27% report persisting symptoms after 30 days, among which 6% were hospitalized at onset. Long-COVID symptoms include fatigue (54%), anosmia/ageusia (40-43%), shortness of breath (27%), cognitive difficulty (39%), muscle/bone complaints (21-25%), and anxiety/depression (19-25%). Females (29%) and those over 50 years (34%) are more likely to be affected.

**Conclusion:** Almost 30% report symptoms of long-COVID. These symptoms can be debilitating and interfere with daily life, especially in those at highest risk: females and individuals over 50 years. Long-COVID may persist and increase the risk of long-term health problems, which will be studied as we follow individuals up to a year.

<table>
<thead>
<tr>
<th>Participant Characteristics</th>
<th>No symptoms &gt;30 days</th>
<th>Symptoms persisting &gt;30 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>509 (73%)</td>
<td>187 (27%)</td>
</tr>
<tr>
<td>Female sex</td>
<td>341 (71%)</td>
<td>142 (29%)</td>
</tr>
<tr>
<td>Male sex</td>
<td>168 (79%)</td>
<td>45 (21%)</td>
</tr>
<tr>
<td>Age &gt;50</td>
<td>158 (66%)</td>
<td>81 (34%)</td>
</tr>
<tr>
<td>Age &lt;50</td>
<td>351 (77%)</td>
<td>106 (23%)</td>
</tr>
<tr>
<td>Hospitalized for COVID-19</td>
<td>15 (56%)</td>
<td>12 (44%)</td>
</tr>
<tr>
<td>Not hospitalized for COVID-19</td>
<td>494 (74%)</td>
<td>175 (26%)</td>
</tr>
<tr>
<td>Time since positive test (months)</td>
<td>4.2 (2.5, 9.8)</td>
<td></td>
</tr>
<tr>
<td>Time since symptom onset (months)</td>
<td>4.5 (2.6, 10.4)</td>
<td></td>
</tr>
</tbody>
</table>
Patient Reported Experience of Virtual Cancer Rehabilitation during the COVID-19 Pandemic:
A Quality Improvement Project

BACKGROUND: The Cancer Rehabilitation and Survivorship (CRS) program at the Princess Margaret Cancer Centre is a multidisciplinary consultative program that provides rehabilitation services to cancer survivors. Due to the COVID-19 pandemic, the CRS program transitioned its in-person rehabilitation to virtual visits. PURPOSE: (1) Understand the experiences of patients receiving virtual cancer rehabilitation; (2) Describe patient preferences regarding virtual versus in-person cancer rehabilitation; (3) Provide recommendations to inform care delivery moving forward. METHODS: Patients (n = 350) who have received ≥1 virtual services from CRS in the past 3 months were invited to participate in a web-based survey. The survey collects demographic information, feedback on the quality and accessibility of the virtual care received, and preferences for future care delivery.

PRELIMINARY RESULTS: To date, n=107 patients completed the survey (30.57%), with the majority receiving care via videoconferencing (67.29%, 72/107). 47.25% (43/91) of patients indicated a preference for virtual care over in-person care following the COVID-19 pandemic, whereas 29.67% (27/91) indicated otherwise. Visits requiring more physical support (versus emotional) had the highest rates of preference for virtual care (i.e., physiatry visits). Open-ended questions revealed that virtual care was an acceptable alternative in some circumstances, with factors such as personal choice, emotional impact, feasibility, accessibility, and safety being taken into consideration.

CONCLUSION: Patients’ preferences regarding in-person versus virtual care varied based on factors including visit type and extent of emotional support required for the visit. Several recommendations can be made to adapt a patient-centered delivery of cancer rehabilitation care at the CRS program.
**Bioprinting Human Stem Cell-laden Extracellular Matrix Hydrogel for Autologous Skin Analogue Bioengineering**

Autologous split-thickness autograft is still the current standard of care for Severe burn injuries with full-thickness skin wounds however, the availability of healthy donor skin to cover the wound is often limited, resulting in a lengthy hospital stay with increased risk of complication (1). A potential solution is to bioengineer skin analogs through extrusion-based bioprinting. Decellularized extracellular matrices (dECM) containing factors to support cell growth and tissue maturation can be used for the development of bio-ink, which can be further bio-printed into sheets to cover the wound. We hypothesize that extrusion-based bioprinting can be utilized to print skin analogues using burn-derived mesenchymal stem cells (BD-MSCs) incorporated within a biocompatible porcine skin dECM (ps-dECM) bio-ink. We aim to develop a decellularization procedure to generate ps-dECM bio-ink and characterize in vitro properties, as well as establish a lab-developed bioprinting platform for proof-of-concept bioprinting the ps-dECM bio-ink. The histological, morphological, temperature responsiveness and biocompatibility assessments of the ps-dECM bio-ink have been characterized in vitro, utilizing H&E/trichrome staining, live/dead cell staining, and MTS cell proliferation assays. Total collagen content was quantified. The residual DNA was assessed via DAPI staining. A lab-developed bioprinting platform and bio-ink extrusion head was fabricated for bioprinting of ps-dECM bio-ink. The ps-dECM derived bio-ink was successfully developed, reserving >40% of collagen content with all DNA content eliminated. The human fibroblasts showed increased proliferation rate for 14 days after incorporated into ps-dECM while maintaining their cell viability. 5x5 mm and 5x10 mm rectangular patches can be printed with the developed ps-dECM bio-ink using the developed extrusion-based FRESH bioprinting platform (2). With the ps-dECM bio-ink and bioprinting platform, the next step is to assess rheological and mechanical properties of the bio-ink and construct biolayer skin substitutes containing BD-MSCs and keratinocytes.

**References:**

Assessing the Relationship Between Health Outcomes and Ethnic Concentration in Patients with Childhood-Onset Systemic Lupus Erythematosus

Background/Purpose: Adolescents with childhood-onset Systemic Lupus Erythematosus (cSLE) often face challenges in managing their disease and their mental health. Further, there are known disparities in disease severity and health outcomes among nonwhite children with cSLE. However, there is sparse data on the effects of ethnic concentration on cSLE health outcomes. This study examined the relationship between ethnic concentration of patients with cSLE and disease activity, disease damage, and comorbid psychiatric diagnoses.

Methods: We conducted a retrospective cohort study of patients under 18 years old who are diagnosed with cSLE meeting ACR/SLICC criteria and were seen at the Lupus Clinic at SickKids between July 1, 2018, to July 1, 2020. Ethnic concentration, a dimension of the Ontario Marginalization Index, is an area-based measure of the concentration of visible minorities and new immigrants in an area. We performed multivariable logistic regression analysis to examine associations of ethnic concentration with presence of active disease (average SLEDAI-2K score > 4), disease damage (SLICC/ACR damage index >0), and comorbid psychiatric diagnosis.

Results: Table 1 displays disease characteristics. Multivariable logistic regression models did not show an association between ethnic concentration and active disease (OR=1.12, 95% CI=0.79-1.59) or disease damage (OR=1.03, 95% CI=0.71-1.48). Ethnic concentration was associated with a lower presence of psychiatric comorbidities (OR= 0.71, 95% CI= 0.49-1.04), although not statistically significant.

Conclusions: Further research is required to investigate the relationship between ethnic concentration and psychiatric comorbidities to identify possible disparities in reporting mental health illnesses between ethnic groups.

Table 1. Disease Characteristics in Adolescent Patients with cSLE (n=179).

<table>
<thead>
<tr>
<th>Disease Characteristics</th>
<th>Total Cohort (n=179)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease activity during observational period (SLEDAI-2K), median (IQR) (n=178)</td>
<td>2.6 (0.7-5)</td>
</tr>
<tr>
<td>Presence of active disease (SLEDAI-2K &gt;4), n (%) (n=178)</td>
<td>52 (29 %)</td>
</tr>
<tr>
<td>Presence of damage on SLICC Damage Index (score &gt;0), n (%) (n=177)</td>
<td>34 (19%)</td>
</tr>
<tr>
<td>Presence of Severe Disease (CNS disease or nephritis) (ever), n (%)</td>
<td>79 (44%)</td>
</tr>
<tr>
<td>Comorbid Psychiatric Diagnosis (ever), n (%)</td>
<td>37 (21%)</td>
</tr>
</tbody>
</table>
The Role of Molecular Biology in Cold Lung Preservation

**Background:** Lung Transplantation (LTx) is an established therapy critical to treat cases of end-stage lung disease. Currently, lungs are stored at about 4°C after harvest until the beginning of transplant, while recently, optimal preservation temperature was shown as 10°C due to significant temperature-dependent molecular changes.

**Hypothesis:** In this study, we aim to elucidate Parkin levels, an E3 ubiquitin ligase involved in mitophagy, and cytokines (TNF-α, IL-6, IL-8 & IL-1β) in preserved pig lung tissue. These levels were determined at various temperatures, hypothesizing optimal levels at 10°C.

**Methods:** The experiment was conducted using right and left lower lobes of lungs from pigs. We examined levels of Parkin in a control lung: post-harvest (PH) and post-transplant (LTx), in lungs preserved at 4°C: PH, post-preservation (CIT) and LTx, and at 10°C preservation: PH, CIT and LTx. Cytokines were analysed in LTx upper and lower left lung tissue samples. The tissue was lysed, protein extracted, enzyme-linked immunosorbent assay (ELISA) run, levels of Parkin and cytokines measured then normalized to bicinchoninic acid (BCA) assay.

**Results:** Results found significant levels of Parkin only in the LTx groups (normalized, pg/mg). Within LTx, although the levels of Parkin were similar between the different temperatures, there was comparatively less variability in results at 10°C. Cytokine data is pending.

**Conclusions:** Parkin stability at 10°C stipulates stable mitochondrial health. These results evidence better mitophagy at 10°C, indicating that Parkin plays a role in the success of lung preservation at specific temperatures. This will enable future incorporation of mitophagy into lung transplantation.

**References:**

**Background/Purpose:** The enzymes Fp deacytelase and Fp galactosaminidase (Azymes) can remove histo-blood group A antigens (A-ag), converting blood type A human organs to type O. However, the presence of endogenous ABH-glycosyltransferases can potentially regenerate the cleaved A-ag. Notably, lung tissue studies show a higher density of surface A-ag in A1 tissue subtype than in non-A1 counterparts, suggesting these tissues should be examined separately. Herein we conducted an in-vitro time study to examine the re-expression kinetics of A-ag in A1 and non-A1 macrovascular tissue after its removal by Azymes.

**Methods:** Human aortic endothelial cells (HAECs) were isolated from blood type A1, Non-A1 and O lung donors. Cells from each donor were separated into control and treatment groups. After 5-14 days in culture the cells were treated with STEEN solution (control) or STEEN solution + Azymes (treatment). A novel quantification method was used to analyze A-ag expression on HAECs: Samples were collected at 5 timepoints and stained with fluorophore-conjugated anti-A antibody and Hoescht. The density of cell surface A-ag was analyzed using a novel algorithm on image analysis software.

**Results:** 1. In line with previous lung tissue studies, histo-blood group A1 A-ag expression was higher than non-A1 counterparts on human aortic endothelial cells (HAECs). 2. Azymes successfully cleaved histo-blood group A-ag from HAECs after one hour of exposure. 3. A-ag slowly re-expressed in HAECs over 96 hours after treatment with Azymes.

**Conclusions:** This study helped to establish a novel and reproducible method for quantification of A-ag expression in HAECs.
NETOSIS as a Biomarker to Predict Lupus Nephritis Response to Treatment

**Introduction:** Lupus nephritis (LN) is a complication of Systemic Lupus Erythematosus (SLE) occurring in up to 65% of SLE patients. One-third of LN patients do not respond to conventional therapies, leading to a need for kidney replacement therapy, however, there are no biomarkers to stratify the patients regarding their treatment response. We propose to use serum levels of Neutrophil extracellular traps (NETS) at the time of LN flare up as a biomarker to stratify patients regarding their response to conventional treatment.

**Hypothesis:** Serum levels of NET complexes at the onset of LN flare can predict response to conventional treatment.

**Methods:** This is a retrospective, observational study, performed in a prospectively followed cohort of 100 patients. All patients had a LN flare, 82 of which are paired with a kidney biopsy +/- 3 months from the LN flare. All subjects have stored serum in our biobank +/- 3 months from the flare and have completed at least 2 years follow-up after the flare. From the 100 patients with serum at diagnosis, 61 patients have a second serum sample 12 +/- 3 months after the first serum sample. Renal outcome at 12 and 24 months after the LN flare will be defined as complete response, partial response and no response based on creatinine levels and protein levels in the urine. The data then will be analyzed for the predictive power NET complexes in the blood for the response to conventional treatment.

**Results and conclusions:** This is an ongoing study.
Heterogeneity and Cell-Cell Interactions in Clear Cell Renal Carcinoma (ccRCC)

Introduction/Background:

Clear cell renal carcinoma, a type of renal cancer characterized by genetic mutations causing an upregulation of hypoxic pathways, provides a unique opportunity for study. It has a poor response to chemotherapy, but a strong response to specific immunotherapies.

Purpose:

Use single-cell genomics data gathered from multiple tumour samples to better understand the heterogeneity in ccRCC tumours and the cell-cell interactions that take place in the tumour microenvironment (TME).

Methods:

Individual cells from tumour samples are barcoded using 10X Single-Cell Genomics technology. Cells are run through an RNA sequencing process and a cDNA library; resulting in a matrix that identifies the level of relative gene expression for each cell.

Results:

The matrix and biomarker genes obtained from the aforementioned process allows for cluster analysis to identify different cell types in the TME. Some examples of broad labels include myeloid, endothelial, lymphocyte cells. These broad labels are further broken down into fine clusters such as cytotoxic lymphocytes or helper-T lymphocytes. The relative level of gene expression can also be used to describe the type and amount of cell-cell interactions that take place in the TME.

Conclusion:

Much insight into the heterogeneity and the cell interactions that occur in the TME of ccRCC has been gained. More information about the TME is required to draw any meaningful conclusions from the data, as such, the team is looking into grading the tumour samples according to the Fuhrman grading scale by using immunofluorescence.
Regionalization of Quiescent Versus Primed to Proliferate Retinal Stem Cell Populations in the Mouse Ciliary Epithelium

Retinal stem cells (RSCs) are rare, quiescent cells located in the ciliary epithelium (CE) of the adult mammalian eye. The lack of molecular markers available to characterize the RSC population has posed significant challenges to identifying RSCs in vivo and understanding RSC function. Recently, we performed single cell RNA deep sequencing on primary ciliary epithelia enriched 1:3 for RSCs, revealing that RSCs can be clustered into 2 distinct populations based on their transcriptomic signature; a quiescent population and a primed to proliferate population. Bioinformatic analysis to detect differential gene expression between the two RSC populations revealed several candidate genes enriched in one cluster over the other. Here, we focus on transcription factor Hdac10 and receptor Cnr1 which are both enriched in the quiescent RSC population. To validate our transcriptomic data, we performed fluorescent in situ hybridization to visualize Hdac10 and Cnr1 mRNA expression within the CE. mRNA staining was consistent with our transcriptomic data, and most interesting showed that Hdac10 and Cnr1 localized in the portion of the CE most distal from the retina. Preliminary evidence shows that genes enriched in the primed to proliferate RSC population regionalize in the CE more proximal to the retina. This may suggest that the adult RSC niche is a remnant of development where RSCs that were less proliferative during development remain distal to the retina in a more quiescent state during adulthood and may represent a more potent RSC population that can be targeted for regenerative therapies.
Genomics of Radiation Resistance in Meningiomas

Meningiomas are the most common primary brain tumour in adults. First-line therapy is often surgical resection for symptomatic meningiomas. Select patients, often with higher WHO grade (2, 3) meningiomas, receive adjuvant fractionated radiotherapy (RT). Some clinically aggressive meningiomas still recur early, requiring repeat operations. It is likely, the reliance of the WHO grade on histopathology fails to capture the tumours’ heterogenous biology and molecular alterations exist that contribute to RT resistance and RT sensitivity in meningiomas.

We aimed to investigate differences in genome-wide DNA methylation and RNA expression profiles of RT responsive versus unresponsive meningiomas. DNA were extracted from tumours and bisulfite converted. Total RNA was isolated from tumour samples. Illumina Infinium MethylationEPIC Beadchip array was used to obtain genome-wide DNA methylation profiles on bisulfite-converted DNA. mRNA libraries were generated and sequenced on the Illumina HiSeq 2500 high output flow cell. We compared differentially methylated regions and expressed genes between RT-resistant and RT-sensitive meningiomas, and progression-free survival between the groups.

Fifty-nine meningiomas were sequenced (27 RT-resistant and 31 RT-sensitive) with no significant difference in the proportion of WHO grade 1, 2, and 3 tumours among groups. Mean progression-free survival was 7.26 years (95% CI 5.27-9.27) in the RT-sensitive group compared to 2.22 years (95% CI 1.72-2.71, p<0.001) in the RT-resistant group. Unsupervised consensus clustering based on both differentially methylated regions and expressed genes demonstrated significant differences in epigenetic and RNA expression profile between these groups.

There are notable differences in the molecular features of meningiomas that respond to RT and those that do not, superseding the current WHO classification. Analysis of the molecular features of RT-resistant meningiomas may uncover novel therapeutic vulnerabilities for these tumours.
Determination of possible inhibitors for the neurolysin enzyme

A subset of patients with acute myeloid leukemia (AML), overexpress the zinc metallopeptidase, neurolysin (NLN), a mitochondrial matrix enzyme that regulates oxidative phosphorylation and mitochondrial metabolism. Inhibiting NLN disrupts mitochondrial function and kills AML cells in vitro and in vivo while sparing normal cells. Here we characterized the enzymatic activity of NLN cell free assays as a step towards developing a high throughput screen for small molecule NLN inhibitors.

We determined that NLN cleaved the fluorescent peptide substrate, PLGPK-AMC, with a Km of 27.8uM. As a positive control for an NLN inhibitor, we showed that the small molecule, R2, inhibited NLN enzymatic activity with an EC 50 of 119.35. In contrast, proteasome inhibitors of the mitochondrial matrix protease ClpXP had no effect on NLN activity. NLN has a metallopeptidase containing zinc. To determine whether zinc is necessary for NLN’s peptidase activity, we treated NLN with the chelators, EDTA and EGTA. EDTA and EGTA inhibited NLN’s peptidase activity, demonstrating the requirement for zinc. Finally, we established a high throughput assay for NLN inhibitors that had a Z score of 0.789.

Thus, we have characterized the enzymatic activity of NLN and developed an assay that can be used to screen for NLN inhibitors.
The master regulator of inflammation STING is upregulated in the kidneys of comorbid diabetic mice with acute kidney injury

**Background:** People with diabetes are more likely to develop acute kidney injury (AKI) than people without diabetes. However, whereas several management strategies exist to slow the progression of chronic kidney disease in diabetes, there are no specific treatments for AKI beyond supportive care.

**Purpose:** To identify key molecular pathways which augment AKI development in diabetes.

**Methods:** Mice were fed a high fat diet for 26 weeks and received a single dose of streptozotocin to induce diabetes after 12 weeks (DM-HFD mice). AKI was induced by ischemia reperfusion injury (IRI; bilateral clamping of the renal pedicles), with assessment of function (plasma BUN and creatinine) and structure (H&E staining) 24h later. Nanostring nCounter was used to quantify inflammatory gene mRNA levels. Expression of genes of interest was probed for by qRT-PCR and immunoblotting.

**Results:** Plasma BUN and creatinine and kidney tubule injury were each increased in DM-HFD mice with IRI in comparison to sham-operated DM-HFD mice and non-diabetic mice with IRI. 54 of 248 inflammatory genes were differentially expressed in DM-HFD IRI kidneys. We speculated that the upregulation of multiple inflammatory genes in kidneys of DM-HFD mice with IRI is indicative of master regulator gene dysregulation. Accordingly, we found that both mRNA and protein levels of the master regulator of inflammation STING were increased >4-fold in the kidneys of DM-HFD mice with IRI.

**Conclusion:** Kidney expression of the pro-inflammatory master regulator STING is increased in mice with comorbid diabetes and AKI. Therapeutic targeting of STING may improve AKI outcomes in diabetes.
Developing an electronic intermediary device to control a wheelchair using a brain-computer interface to increase mobility and independence for those with disabilities

Individuals with tetraplegia often require a wheelchair device for mobility. However, they can be limited in their ability to control the wheelchair which reduces their mobility and limits their independence. The intent of this research project is to develop a mechanism to control a wheelchair using electrical activity from the brain.

The power wheelchair used in this project is controlled under the single switch scanner setting; Pushing a single button, a user can move the wheelchair in any direction. We sought to modify this mechanism to control the wheelchair using a brain-computer interface (BCI).

Using Bluetooth Low Energy and two Arduino microcontrollers boards, we developed a mechanism to send a signal wirelessly that closes a circuit. This is an initial step in developing a device in which brain electrical activity can control the motion of a wheelchair. Next, we intend to attach the BCI to the Arduino board. Brain activity will be measured through Electroencephalogram (EEG) and analyzed by the BCI. When the BCI detects a movement attempt it will send a signal to an Arduino. Using Bluetooth Low Energy, this Arduino can transmit the information to the second Arduino that is able to activate a switch acting as the wheelchair single switch button. The wheelchair receives the signal and moves accordingly. The wireless communication ensures the device’s safety and flexibility.

Thus, we are developing a device that may improve the mobility of those with disabilities such as tetraplegia.
Serial MRI imaging of mice after unilateral nephrectomy reveals unsuspected heterogeneity in compensatory renal growth response

**Background:** Unilateral nephrectomy (UNx) is expected to trigger compensatory renal growth (CRG) of the remnant kidney, with a concomitant increase in function. CRG is key following living kidney donation to ensure adequate long-term renal function; however, ~20% of donors do not experience CRG, placing them at risk for chronic kidney disease. A better understanding of the CRG process is critical to maximize donor CRG; to this end, animal models are used whereby CRG is induced by UNx. Most studies assess CRG 14 days post-UNx by comparing wet kidney weights of the remnant kidney to the nephrectomized kidney of the same mouse or the ipsilateral kidney of control mice, thus relying on invalid assumptions.

**Hypothesis:** We hypothesize that serial magnetic resonance imaging (MRI) of mice up to 28 days post-UNx is a more accurate measure of CRG than “wet-weight” approaches.

**Methods:** Male mice underwent either left UNx, left sham surgery (kidney externalized), or no surgery. MRI was performed on days 0, 3, 7, 14, and 28 and three coders calculated kidney volumes. Kidney function was assessed by serum creatinine measurements.

**Results:** UNx-mice undergo CRG, as revealed by a large increase in kidney volume from day 0 to 28. The variance in CRG trajectories within and between mice suggests that the CRG response is highly heterogenous; therefore, CRG at earlier timepoints does not predict the degree of CRG at day 28. Comparing the “wet-weight” approach to real growth reveals that the former overestimates the CRG response.

**Conclusion:** This non-invasive serial imaging approach to measure CRG allows for longitudinal kidney volume measurement, eliminating the need for invalid assumptions used in “wet-weight” approaches.
To investigate the prevalence of fatty acid metabolites in the serum of psoriatic arthritis patients by utilizing solid-phase microextraction, liquid chromatography and high-resolution mass spectrometry

Psoriasis (PsC) is a relatively common inflammatory disease which affects over one million people in Canada and approximately 125 million people worldwide\(^1\). Approximately 25% of psoriasis patients have an inflammatory arthritis termed as psoriatic arthritis (PsA) that affects multiple organ systems such as skin, nails, peripheral and axial joints, and lead to by a reduced quality of life and function\(^2,3\). The purpose of this study is the development of a qualitative, targeted lipidomic method to determine potential serum biomarkers in PsA patients and its ostensible association with joint and skin related activity in PsA patients. 78 Serum samples from PsA, PsC and Healthy Controls with established diagnosis were collected using Solid Phase Micro-extraction (SPME) to build a biomarker-discovery cohort and were analysed using a Liquid Chromatography - High Resolution Mass Spectrometry (LC-HRMS) machine. Metabolite concentrations were calculated from the obtained spectra to build diagnostic models for subsequent statistical analysis on the software – MetaboAnalyst 5.0\(^4\). The generated univariate model was employed to establish differences between potential metabolites in PsA and PsC patients. While significant metabolite differences were observed in the univariate model, validation in larger multi-ethnic cohorts would deem this diagnostic model as a valuable tool for a definite diagnosis of PsA patients. However, further exploration is necessary for identification and validation of metabolomic biomarkers which may accurately and reliably predict which psoriasis patients will develop psoriatic arthritis and measure psoriatic arthritis disease activity in affected individuals.

Keywords – Psoriasis (PsC), Psoriatic Arthritis (PsA), biomarkers, Solid Phase Micro-extraction (SPME), Liquid Chromatography - High Resolution Mass Spectrometry (LC-HRMS), Statistical analysis, MetaboAnalyst 5.0, Metabolomics.

References:
Mapping the Hypermetabolic Response in a Severe Burn Patient

**Background:** A severe burn injury results in a hypermetabolic response, which is associated with chronic increases in markers of inflammation, catabolism and resting energy expenditure (REE), which may persist for up to 2 years post-burn. Currently, therapeutics aimed at reducing post-burn hypermetabolism lack specific timelines for intervention.

**Purpose:** The aim of this study was to develop a roadmap of biomarkers elevated at certain timepoints post-burn, which could help improve outcomes in patients with severe burns.

**Hypothesis:** We hypothesize that markers of inflammation are elevated at early time points whereas markers of catabolism exhibit a delayed increase.

**Methods:** Adult burn patients admitted to the Ross Tilley Burn Centre at Sunnybrook Hospital from 2010-2020 were retrospectively included in this study. Patients were selected based on the inclusion criteria of 18-65Y and those ≥20% total body surface area burns. Subcutaneous adipose tissue samples were collected during scheduled surgeries. Gene expression was measured using RT-qPCR and a multiplex assay was used to measure circulating cytokine concentrations in patient plasma samples.

**Results:** There was a significant correlation (p<0.0001) between increasing Ucp1 mRNA expression, a marker of adipose tissue catabolism, and days post-burn. REE was consistently elevated in comparison to the average REE of a non-burn individual however remains stagnant following days post burn. IL-6, MCP-1, and IL-10 was greatly elevated within the first 7 days post burn.

**Conclusions:** The rapid increase in cytokine concentrations of IL-6, MCP-1, and IL-10 may be used as early determinants of the pathophysiological response in burn injury.
Inhibition of the mitochondrial unfoldase-peptidase complex, ClpXP, by phosphorylated serine and threonine

Aberrant mitochondrial proteostasis is characteristic of a diverse subset of malignancies ranging from hematological disorders to solid tumours. Consequently, mitochondrial proteins have garnered significant attention as promising therapeutic targets. One such protein is ClpXP, a matrix protease complex responsible for degrading damaged and misfolded proteins to maintain the integrity of the mitochondrial respiratory chain and mitochondrial metabolism. Overexpression of ClpXP has been frequently reported in cancers such as AML that have increased reliance on oxidative phosphorylation.

The bacterial homolog of ClpXP degrades proteins marked with a phosphoarginine tag, but the tags that mark proteins for degradation by human ClpXP are unknown.

Using fluorescent cell-free kinetic assays, we discovered that phosphoserine and phosphothreonine but not phosphotyrosine or phosphoarginine inhibit ClpXP activity. Free serine, threonine and phosphate also had no effect on the enzyme’s activity. Thus, our work suggests that phosphoserine and phosphothreonine mark proteins for degradation by ClpXP. Additionally, titrating substrate into different treatments of phosphoserine did not alter the relationship between Vmax and Km, indicating an uncompetitive/mixed mechanism of inhibition.

References:

Hearing Outcomes of Implantable Bone Conduction Devices from 2000-2021: A Retrospective Study of 194 Children

Introduction: Children with hearing loss who are unable to use conventional hearing aids and/or become candidates for cochlear implantation can gain access to sound with bone conduction devices. These devices help stimulate the inner ear (cochlea) through skull vibration. Implantable bone conduction devices have progressed historically from percutaneous to passive transcutaneous and, most recently, active transcutaneous options, reducing complication rates over the past 20 years.

Purpose: This study will assess hearing outcomes in one of the largest followed cohorts of children with bone conduction implants, based on factors such as hearing loss type and device change.

Methods: A retrospective chart review of 194 children at the Hospital for Sick Children who received implantable bone conduction devices between November 2000 and May 2021 was completed. Audiometric thresholds were collected in response to sound presented through bone conduction, and acoustically (air conduction) with or without use of the bone conduction device. Data were plotted and analyzed in RStudio v.4.1.0.

Results: Most of the cohort (140/194, 73%) received percutaneous unilateral devices; of these children, most (111/138, 87%) had bilateral hearing loss involving the outer and/or middle ear (conductive). Remaining children had mixed bilateral hearing loss or hearing loss in only one ear (conductive or sensorineural). After implantation, children gained access to conversational sound, but hearing sensitivity did not quite reach the potential measured by bone conduction thresholds (Aid-Bone = 11.97 ± 10.35 dBHL).

Conclusion: Bone conduction devices improve hearing in children, however do not reach potential bone conduction thresholds.

Characterization of function and expression of the autism risk factor gene PTCHD1

Diagnoses of autism spectrum disorder (ASD), a neurodevelopmental condition that is associated with social impairments, have been increasing over the last several decades. The X chromosome-encoded gene Patched domain-containing 1 (PTCHD1) has been associated with ASD in male patients. The current study examines different aspects of PTCHD1, aiming to acquire a greater understanding of its expression and function in a neuronal context. We first sought to measure endogenous Ptchd1 protein in vitro by utilizing CRISPR/Cas9 and homology-directed repair to generate mouse embryonic stem cell (mESC) lines with a canonical peptide tag (3xFLAG) fused to the Ptchd1 coding sequence. N- and C-terminal 3xFLAG-Ptchd1 fusion cell lines were differentiated into neurons over a period of 17 days using retinoic acid, followed by immunoprecipitation of the recombinant fusion proteins from the neuronal lysates and subsequent western blotting. In addition, as function is highly correlated with expression, this study next endeavored to validate a putative 8 Kb regulatory region that is located approximately 17 Kb downstream of Ptchd1. Deletion of this genomic region in mESCs by CRISPR/Cas9 increased Ptchd1 expression by over 50% in both mESCs and neurons, suggesting the possible presence of silencer elements. Lastly, we investigated the alleged interaction in vitro of PTCHD1 with the pre-synaptic SNARE-associated protein (SNAPIN), and if any potential association is mediated by the C-terminal PDZ-binding domain of PTCHD1. This was examined by transiently overexpressing tagged versions of both PTCHD1 (wildtype and p.I885*) and SNAPIN into HEK293T cells, followed by co-immunoprecipitation and western blotting. Collectively, these results will provide critical insights regarding the expression, stability and function of PTCHD1. These findings are important for obtaining a greater understanding of neuronal dysfunction in ASD, which will assist in the development of novel therapeutic treatments.
Assessment of Biologic Therapy Dosing Schedules and Duration of Efficacy in Asthma: A Pilot Study

**Background:** Injectable biologic therapies, spaced anywhere from 2 to 8 weeks apart, have revolutionized the management of severe asthma. Anecdotally in clinical practice, some patients have reported worsening asthma symptoms near the end of their dosing interval, in what may be a trough effect of these biologics. The Asthma Control Questionnaire (ACQ-6) is a validated asthma control tool for research and clinical practice, with a one-week recall of 5 asthma symptoms and the need for a rescue bronchodilator. A change in ACQ-6 score of greater than or equal to 0.5 is the accepted minimal clinically important difference (Barnes et al., 2014).

**Purpose:** To determine whether a trough effect exists for biologics in severe asthma and identify factors associated with the phenomenon.

**Methods:** 55 patients currently receiving omalizumab, mepolizumab, benralizumab, or dupilumab were recruited from a single site using the International Severe Asthma Registry. Each patient completed the ACQ-6 over the phone on two occasions - in the first half and the final week of their dosing interval. Patients were blinded to the hypothesized trough effect and were informed they were helping validate the ACQ-6 as a telehealth questionnaire over time. Baseline patient demographic information, including age, sex, BMI, Forced Expiratory Volume in 1 second (FEV1), comorbidities and smoking status, were obtained from the electronic medical record. Paired t-tests were performed to compare ACQ-6 scores from the first half and last week of the dosing interval. Two-sample t-tests were used to compare changes in ACQ-6 scores in subgroup analyses.

**Results:** Preliminary data from 28 patients with severe asthma on biologic therapy demonstrate no significant difference in ACQ-6 scores between the last week and first half of the dosing interval (mean difference 0.121 [95% CI -0.147, 0.123; p=0.854]). No significant differences in ACQ-6 scores were demonstrated in subgroup analyses by age, sex, BMI, FEV1, biologic or injection type.

**Conclusions:** In patients with severe asthma on biologic therapy, there is no demonstrable trough effect of asthma control towards the end of the dosing interval. Further study with larger sample sizes may confirm this finding or reveal subgroups that are more likely to experience this phenomenon.

**References**

An evaluation of the Cancer Rehabilitation and Exercise - Advanced Cancer (CaRE-AC) program

Background: Patients with advanced cancers (AC) face complex challenges, including fatigue, pain, reduced physical mobility, and impaired psychosocial function (1). Early research suggests the importance of physical rehabilitation for AC patients, but high-quality evidence on its safety, acceptability, and efficacy is still needed.

Purpose: To assess 1) the feasibility and acceptability of the CaRE-AC program at Princess Margaret Cancer Centre and 2) preliminary effects on patient-reported and objective outcomes.

Methods: Design: Mixed methods pre-post Phase 1 study. Intervention: CaRE-AC is an 8-week multidimensional, group-based program incorporating exercise and self-management skills teaching. Assessments: Participants undergo initial physical assessments with re-assessments at 8-weeks (T1), 1 (T2), 3 (T3), and 6-months (T4) post-intervention. Qualitative data from semi-structured interviews were collected at T1. Quantitative data included patient-reported outcomes (quality of life, fatigue, social functioning) and physiological factors (fitness, muscle strength, BMI).

Results: 58 patients were referred to the CaRE-AC program between March 2019 and March 2020. 36 patients completed the initial assessment, 22 completed it at T1 (61%), and 13 completed it at T4 (36%). Measures of physical function at T1 demonstrated trends towards improvement through T4. Interviews and questionnaires confirmed acceptability of the program. Institutional factors (location, facilitators, accessibility), the curriculum (educational and physical), interpersonal relationships and perceived long-term benefits emerged as key themes.

Conclusion: The CaRE-AC program was acceptable to patients, with a 61% completion rate. Feedback can refine program content and delivery. Future research involving larger cohorts is necessary to assess cancer and patient-specific factors that may influence program response.

Electric Field Stimulation for Neural Repair: Activating Endogenous Neural Precursor Cells

Introduction: Stroke is a leading cause of death and disability worldwide. There are currently no therapies that repair the injured brain following stroke. Neural stem cells and progenitor cells (together termed neural precursor cells, NPCs) that reside in the subventricular zone (SVZ) of the brain have the potential to provide new cells to replace those lost to injury. NPCs are electrosensitive cells that respond to endogenous electric fields (EFs) generated in vivo. We propose that applied EF stimulation can promote migration to sites of injury and promote neural repair. Indeed, we have shown that clinically relevant biphasic monopolar EF stimulation can activate NPCs and induce their neuronal differentiation, migration, and survival both in vivo and in vitro.

Purpose: Herein, we propose using an ex vivo model to optimize the stimulation parameters for NPC stimulation. The novel ex vivo model will provide a relatively high throughput system in which to examine NPC activation, as a first step to in vivo application. To validate our ex vivo model, we will compare the results of this model to the in vivo model, using the same stimulation parameters. We would expect that the application of these EFs would induce a migration of NPCs in our ex vivo model similar to what was observed in vivo.

Methods: We isolated 1mm murine brain sections, containing the SVZ, and stimulated across the corpus callosum for 3 hours at 500 mV. Sections were fixed and cryosectioned, and immunohistochemistry was performed for migrating neuroblasts (doublecortin positive, DCX+) which were examined in stimulated and unstimulated brain sections. The distance of the cells from the dorsolateral corner of the SVZ was used as a measure of migration, and the total number of DCX+ cells was counted as a measure of NPC expansion.

Results: As predicted, the application of EFs on these 1mm tissue sections induced a directed migration in the NPCs along the corpus callosum; however, no change in the number of NPCs was observed.

Conclusion: This moderate throughput ex vivo model is representative of how NPCs respond in vivo, and can thus be used to optimize the parameters of our EF stimulation. These optimized parameters will be used for in vivo stimulation to promote NPC activation and neural repair following injury.
The Restorative Effects of Amnionic Fluid Stem Cell Extracellular Vesicles on Hypoplastic Fetal Rat Lungs at the Canalicular and Saccular Lung Developmental Stages

Introduction
Pulmonary hypoplasia secondary to congenital diaphragmatic hernia (CDH) is characterized by decreased lung maturation via impaired lung epithelial cell and lipofibroblast expression. We recently demonstrated that administration of extracellular vesicles derived from amniotic fluid stem cells (AFSC-EVs) rescues fetal lung development in rodents with pulmonary hypoplasia at the pseudoglandular stage. Herein, we investigated whether AFSC-EV treatment had similar beneficial effects when administered at translationally relevant lung developmental stages.

Hypothesis
AFSC-EV treatment rescues epithelial and mesenchymal cell differentiation in hypoplastic fetal rat lung explants.

Methods
EVs were isolated from rat AFSC conditioned medium by ultra-centrifugation and characterized for size, morphology, and expression of canonical EV-related protein markers. Nitrofen was administered to rat dams at embryonic day E9.5 to induce CDH, those given olive oil served as control. At E17.5 (canalicular) and E20.5 (saccular), dissected fetal lungs were grown as explants with medium alone or AFSC-EVs for 72h. Protein expression and immunolocalization of alveolar type 1 (AGER/PDPN), type 2 (SPC), basal (P63), club (CC10), fibroblast progenitor (PDGFRA) and lipofibroblast (PPARG) cells were assessed using western blotting and immunofluorescence.

Results
At E20.5, all markers except P63 had impaired expression in nitrofen-treated explants. The same expression patterns were observed at E17.5 except for CC10, and PDGFRA levels were upregulated (p<0.05). AFSC-EV administration restored expression levels to control at both gestational ages (p<0.05).

Conclusions
AFSC-EV administration rescues epithelial and mesenchymal cell differentiation at both stages. Further studies will aim to corroborate these findings, which represent a translational opportunity for clinically relevant timepoints for antenatal interventions.
Implementing a Diet & Nutrition Workshop for Cancer Survivors at ELLICSR Kitchen

**Background:** Achieving and maintaining a healthy weight and consuming a nutrient-rich diet are important to improve long-term health and well-being of cancer survivors. However, few are meeting recommended guidelines. To address this, the Cancer Rehabilitation and Survivorship Program is developing a workshop entitled “Feel Good and Improve Eating Habits”.

**Purpose:** To obtain feedback from cancer survivors on the proposed program content and structure in order to inform the final workshop design.

**Methods:** We used a mixed methods approach which included: 1) an anonymous online survey (n=17), and 2) a virtual patient focus group (n=3) with a subset of survey participants. Descriptive analysis of the survey results and thematic analysis of the focus group were performed.

**Results:** Most survey participants (94%) indicated that they would enroll in the proposed workshop. All proposed topics were of interest with highest interest in *Eating well, goal setting, and building a healthy plate* and *Mindful eating and cooking, and smarter snacking*. Respondents preferred a workshop that is 6-weeks (41%) with weekly one-hour sessions (65%). The majority preferred online and asynchronous (59%) delivery that uses combination of PowerPoint presentation and demonstration (59%). Focus group themes included resolving access and affordability barriers with respect to healthy eating, creating a non-judgemental approach to nutrition, and implementing sustainable lifestyle changes.

**Conclusion:** The data provides useful information on workshop format and delivery and has identified important themes/topics that should be integrated into the content. The workshop is expected to be rolled out in Fall 2021.
Thyroid carcinoma is rare in childhood but increases with advancing age, becoming the most common cancer among adolescent females ages 15-19. With appropriate treatment, the prognosis is highly favourable. We aimed to characterize the clinical and pathological features, treatment patterns, and short-term outcomes of thyroid carcinoma among pediatric patients evaluated and treated at a single, high-volume tertiary care hospital. We performed a retrospective cohort study of patients who underwent surgery for thyroid carcinoma at The Hospital for Sick Children between 1986 and 2021. 171 patients were included for analysis. We reviewed surgical pathology reports to gather information on disease extent and patient charts for treatment and outcome variables. Papillary thyroid carcinoma is overwhelmingly the most common type, reflecting 93% of diagnoses. Incidence of thyroid carcinoma has been rising over the study period, though there is large year-to-year variation. A female predominance emerges in adolescence, during which time more females are diagnosed with thyroid cancer than males. Prior to age 10, the Female:Male ratio is 1.2:1, while above age 14, it is 2.6:1. Younger children are more likely to have locoregional and distant metastases. Finally, radioactive iodine treatment has decreased in the last five years, coincident with a change in clinical practice guidelines in 2015 that advocated for limiting the use of radioactive iodine therapy. Knowledge of the landscape of pediatric thyroid malignancy will drive investigations of underlying pathology and may identify opportunities for research on improvement of care and outcomes.
Background: Severe, refractory obsessive-compulsive disorder (OCD) has been shown to be treated successfully with neuromodulatory techniques such as deep brain stimulation (DBS) and radiosurgical lesioning. Curiously, neuromodulation targeted at distinct anatomical regions can be likewise efficacious at reducing symptoms. It is therefore hypothesized that the connectivity of diverse targets to a common brain network is responsible for clinical outcomes, which has been shown previously for other psychiatric disorders. Methods: We harnessed a normative resting-state fMRI connectome to identify the brain network underlying symptom improvement in OCD. Studies treating OCD with neuromodulation were identified in two reviews and the clinical trials registry. This resulted in a comprehensive list of targeting coordinates historically used in neuromodulatory treatment and their resulting efficacies as YBOCS percentage improvement. Functional connectivity based on a normative connectome was seeded from the coordinates to produce functional connectivity maps. Voxel-wise statistical testing produced an average efficacy map of voxels significantly associated with YBOCS improvement. Results: Seventy-five studies were extracted, encompassing four neuromodulatory techniques: DBS, lesioning, transcranial magnetic stimulation, and transcranial direct current stimulation. In the resulting efficacy map, regions associated with ≥35% YBOCS improvement included the midbrain, dorsal anterior cingulate cortex, subcallosal cingulate cortex, orbitofrontal cortex, temporal pole, amygdala, hippocampus, and parieto-occipital area. Conclusions: We elucidated the underlying brain network of clinical improvement following neuromodulation for OCD using target coordinates from published studies. This network-based perspective may improve our understanding of neuromodulation targeting for OCD.
Machine-learning defines and characterizes the grades of trigeminal neuralgia.

**Background:** Trigeminal neuralgia (TN) is a severe type of chronic unilateral neuropathic facial pain condition.\(^1\)\(^-\)\(^3\) Patients with classical TN experience paroxysmal pain that is characterized by a shock-like nature. A proportion of patients may also experience longer bouts of pain, or mention that despite their initial presentation of classical symptoms, their pain has become constant in nature, with burning or dull features.\(^1\)\(^-\)\(^3\) Given patterns of pain expression over time, we hypothesize that TN pain evolves, and may be associated with different pain characteristics. Artificial intelligence (AI) has been applied to the study of TN using advanced imaging data.\(^4\)\(^-\)\(^5\) Here, we use clinical data and machine learning (ML) derived metrics to propose a novel grading system for TN pain.

**Objective:** To evaluate if AI can define and distinguish grades of TN based on clinical data, and to study the correlation between ML derived clinical metrics and duration of surgical response.

**Methods:** A total of 66 classical TN patients treated with Gamma Knife radiosurgery (GKRS) or microvascular decompression (MVD) were included in this study. We used a data-driven approach that combined retrospective clinical data and dimensionality reduction ML algorithms to produce a prediction framework of pain relief duration following GKRS or MVD for TN. Surgical response was defined as ≥50% reduction in pain intensity, and a score of I-III on the Barrow Neurological Institute (BNI) scale. Duration of response was measured until time of pain recurrence, which was defined as reversion to a score of IV-V on the BNI scale, within a five-year follow-up period. Clinical data was one-hot-encoded in preparation for principal component analysis (PCA). PCA was applied to compute novel ‘pain grades’ for TN before and after feature selection. Feature selection was conducted using the Shapley value reconstruction error model to optimize the amount of input features with respect to reconstruction performance. Correlation of principal components (PCs) and duration of surgical response was assessed using the Spearman correlation test, and significance was evaluated using Bonferroni multiple-comparison correction.

**Results:** PCA of raw and feature selected data yielded 19 and 15 PCs, respectively. In both trials, PC1, largely representing TN pain-related variables, showed significant negative correlation with duration of surgical response, \(\rho = -0.48 \ [-0.65 \ -0.28] \ (p = 0.0007)\), and \(\rho = -0.51 \ [-0.67 \ -0.31] \ (p = 0.0002)\), respectively. Supporting that PC1 may be defined as a novel grade metric for TN.

**Conclusions:** In this study, we demonstrate a data-driven approach to derive a novel grading system for TN based on clinical characteristics that significantly correlates with surgical response duration. This framework may provide a foundation for future development of ML-driven, clinical tools for TN assessment and surgical outcome prognostication.

**References**
Evaluating diffusivity metrics along auditory relay points in patients with acoustic neuromas

Objectives: Acoustic neuroma (AN) tumors are among the most common causes of permanent one-sided hearing loss in adults. One-sided hearing loss results from auditory nerve compression at the site of the tumor in the affected ear. Auditory nerve compression and sound deprivation at the entrance to the auditory path limits the treatment options for one-sided hearing loss. Treating this devastating symptom will require targeting markers of central auditory pathway abnormalities. However, traditional diffusion-weighted magnetic resonance imaging (DW-MRI) techniques have not explored changes to the small auditory relay points along the brainstem and subcortex. In this study, we used DW-MRI data to analyze the microstructural integrity of the inferior colliculus and the medial geniculate nucleus. We hypothesized that diffusivity metrics at these auditory relay points would distinguish AN patients with one-sided hearing loss from individuals with normal hearing.

Methods: DW-MRI data was collected from 62 subjects, including 41 surgically naive AN patients with either a left- or a right-sided tumor, and 21 healthy controls with normal hearing (NH). Pure-tone audiometry (PTA) scores from 34/41 AN patients were used to identify ipsilateral and contralateral hearing thresholds. Masks for the inferior colliculus (IC) and the medial geniculate nucleus (MGN) were drawn manually on a population template, and projected to individual diffusion space. Diffusion-tensor metrics were extracted bilaterally from both regions of interest (ROIs) to assess their microstructural properties per subject.

Results: We included 62 subjects, with left- (n = 23; 13 women and 10 men; mean age ± SD: 52.9 ± 6.0 years) and right-sided (n = 18; 9 women and 9 men; mean age ± SD: 51.2 ± 5.9 years) AN patients, and normal hearing (NH) healthy controls (n = 21; 13 women and 8 men, mean age ± SD: 53.0 ± 4.3 years). Mixed model linear regression showed poorer PTA scores at the ipsilateral ear in both left- and right-sided AN patients at each sound frequency (p < 0.05). Preliminary results showed little to no differences in diffusivity metrics either between contralateral and ipsilateral sides at the two ROIs, or between the AN and NH groups. However, only axial diffusivity was significantly lower at the contralateral MGN compared to ipsilaterally in patients with a right-sided AN.

Conclusion: Our preliminary findings suggest that the inferior colliculus and the medial geniculate nucleus do not show structural abnormalities that differentiate AN patients from healthy controls. Future analysis will investigate whether the diffusivity metrics along these auditory relay points relate to the severity and duration of hearing loss in this patient group. Overall, our results point to the importance of considering other gray matter regions throughout the cortex to better understand the implications of one-sided hearing loss for compensatory changes throughout the whole-brain.
The effects of the miR-137 rs2660304 single nucleotide polymorphism on neurite complexity

Introduction: Exosomes derived from human breast milk have been shown to reduce intestinal injury caused by necrotizing enterocolitis (NEC) in neonates\textsuperscript{1,2,3}. However, the underlying molecular mechanisms of exosomes and their effects on the intestinal epithelium remain poorly understood. miRNAs, found abundantly in breast milk exosomes, play a vital role in immune regulation in a variety of diseases\textsuperscript{4}. This study investigates the protective functions of miRNA 148a against intestinal injury characteristic of NEC and aims to identify the molecular pathways involved. We hypothesize that miRNA 148a downregulates the NF-κB pathway via inhibition of Toll-like receptor 4 (TLR4) hence reducing inflammation and intestinal injury.

Methods: Human colorectal adenocarcinoma (Caco-2) cells were seeded on a 12 well plate at cell density of 2 x 10\textsuperscript{5} 24 hours prior to transfection. Cells were treated with 200 μg/mL lipopolysaccharide (LPS) and subsequently transfected with varying concentrations of miRNA 148a mimic for 72 hours. Transfection efficiency was assessed using positive and negative controls. RNA was extracted using TRIzol extraction method and purified. IL-1β and TNFα gene expression levels were measured by qRT-PCR.

Results: LPS-treated cells showed an increase in TNFα and IL-1β expression levels. Production of TNFα and IL-1β was decreased with treatment of miRNA 148a; while remained unaffected by the treatment of the negative control miRNA.

Conclusions: These data suggest that miRNA 148a, found in breast milk exosomes, may have anti-inflammatory properties and should be investigated further for its potential to reduce intestinal injury caused by NEC.

Structural neuroimaging markers of motor recovery in childhood arterial ischemic stroke

**Background:** Childhood stroke leads to significant motor deficits that vary greatly between individuals. Studies in adult and perinatal stroke have demonstrated the ability of structural neuroimaging markers to predict motor outcome.

**Purpose:** This study extends the investigation of such markers to childhood stroke by including the measures of i) structural connectivity, ii) lesion volume, and iii) cortical thickness.

**Methods:** Conventional and diffusion-weighted MRI scans were collected from 11 patients with childhood arterial ischemic stroke and 8 age-matched controls. i) Structural connectivity was extracted from association matrices constructed from T1-weighted parcellations and diffusion tractography. ii) Lesion volume was derived from masks manually traced on T1-weighted images. iii) Cortical thickness was automatically estimated as the distance between the white matter and pial surfaces following cortical reconstruction. Motor outcome was measured using the sensorimotor subscale of the Pediatric Stroke Outcome Measure.

**Results:** Currently, lesion volume has been extracted from $n = 9$ stroke patients. Preliminary analysis on this sample revealed no significant correlation between lesion volume and motor outcome.

**Conclusions:** These results align with the inconsistent relationship between lesion volume and motor outcome reported in the stroke literature. However, conclusions from this preliminary analysis are limited by small sample size. Our next steps will involve calculating structural connectivity and cortical thickness for all participants and exploring the relationship of these measures with each other and motor outcome. These findings will improve our understanding of motor system damage and recovery in childhood stroke with the aim of better guiding prognosis and treatment for patients.
Determining Genes and Pathways Enriched in Antibody-Mediated Rejection

**Background:** Kidney transplantation is the best treatment for end stage kidney disease. However, most kidney grafts are lost prematurely, mainly due to antibody-mediated rejection (ABMR), particularly its chronic form, transplant glomerulopathy (TG). Despite their importance, pathophysiology of ABMR, and particularly TG, are incompletely understood. Insights from the molecular signatures of public datasets may lead to a better understanding of the acute ABMR to TG transition. The **purpose** of my project is to identify the enriched genes and pathways in different forms of ABMR, particularly TG. I **hypothesize** that TG will exhibit an enrichment in genes belonging to innate immune and myeloid cell populations compared to other forms of ABMR or cellular rejection. My **objective** is to examine all available public gene expression datasets relevant to ABMR in human kidney allograft biopsies.

**Methods/Results:** The Gene Source Matrix of all available data (up and down regulated genes in kidney tissue across 32 studies) and 91 GEO Datasets from NephroDIP, an online database transcriptome of kidney transplant recipients, were analyzed. Fourteen studies (4407 samples) were identified as relevant to ABMR or TG. When ABMR was compared to other clinical pathologies, 298 differentially expressed genes were identified (Q<0.05). The top pathways that were significantly enriched and implicated the greatest number of these genes included the immune system (Benjamini Hochberg, Q=1.15323e-30), innate immune system (BH, Q=1.28620e-10), and adaptive immune system (BH, Q=1.97731e-16). There were 25 differentially expressed genes in acute ABMR compared to TG and the top pathways were signal transduction (BH, Q=4.61705e-06), pathways in cancer (BH, Q=2.35121e-11), and EMT regulators (BH, Q=1.26601e-07). The top pathways of the 11 differentially expressed genes in TG versus control included the immune system (BH, Q=1.21469e-03), hemostasis (BH, Q=3.64368e-04), and the innate immune system (BH, Q=2.02368e-03).

**Conclusion:** The immune system, innate immune system, and signal transduction pathways include the greatest number of differentially expressed genes in ABMR or TG across all major comparator groups. I will next examine the pathways and genes significantly altered between TG and other forms of rejection.