8th Annual Child Health and Human Development Program Research Day

November 25th, 2022

In-Person Event

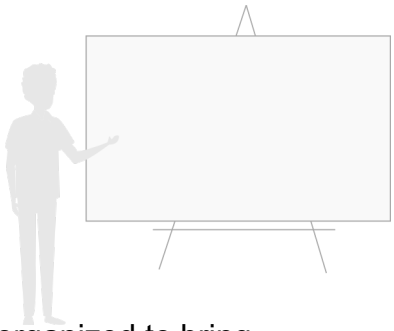
Booklet

Public

Centre universitaire de santé McGill
Institut de recherche

McGill University Health Centre
Research Institute

CHHD
Child Health and Human Development Program



Welcome to the

8th Annual CHHD Research Day

November 25th, 2022

The Child Health and Human Development Program Research Day is organized to bring together the program's members and reinforce collaborations and networking, and create bonds between the members, and for the first time in 3 years, *in person!*
(zoom link provided below for oral presentations and invited speakers-atop the program)

Please note that all attendees, including presenters and judges, should be registered prior to attending the event. If, however, someone does not register, the option to attend via Zoom (see above in red) will be possible. Moreover, lunch will only be provided for registrants.

Registration will allow you to receive all the relevant information and updates prior to the research day, and allows us to know your lunch preferences.

Registration deadline: ***November 20th, 11:59 p.m.***

To register please follow this link below:
https://docs.google.com/forms/d/e/1FAIpQLSdgq0C4icNSG6ae7IK7zN2k7xiFwv-ep4Gc9idKkFer3EYZ2w/viewform

Or go to the research day page in the program's website:
www.chhd-program.com/8th

On the next pages, you will find:

- The research day program including all the links
- Health and Safety Instructions
- The awards list
- Important information for the day
- The abstracts list
- Evaluation forms (for judges and in print only).

If at any moment during the day, you have a question or a problem, please reach out to Martin Karam or Atefeh Masoumipour in person or by email:

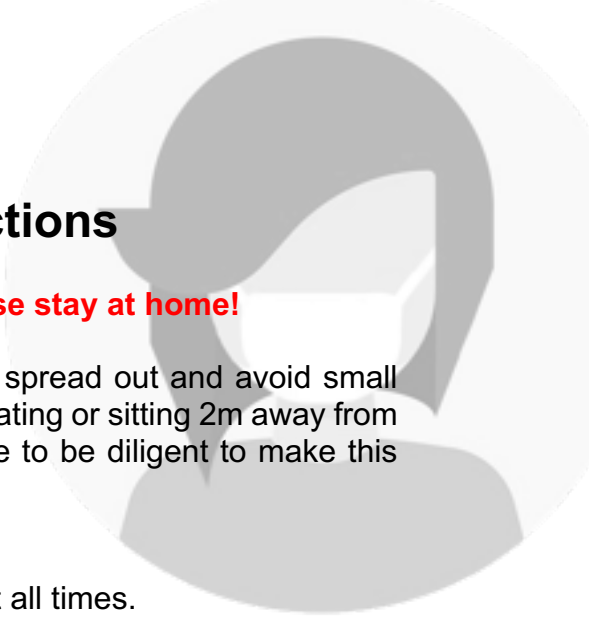
Martin.karam@muhc.mcgill.ca
Atefeh.masoumipour@muhc.mcgill.ca

Research Day Program

Friday, November 25th, 2022 – 8:30 – 17:20

https://us06web.zoom.us/j/88584772492?pwd=RXZhU0dJUUIwSUkzR0NqcmpaRC9mQT09

8:30 - 9:00	Gathering in the auditorium and setting up posters
Welcoming remarks and CHHD updates	
9:00 - 9:10	**Dr. Daniel Dufort**, CHHD Program Leader
CHHD Principal Investigator presentation	
9:15-9:45	**Dr. Teruko Taketo**, CHHD Senior Scientist
Title	The Effects of Sex Chromosome Complement, XX, XO, or XY, on the Female Germ Line Development in the Mouse
Instructions for the day and safety regulations	
9:50-9:55	**Dr. Martin Karam**, CHHD Program Manager
Senior oral presentations sessions (Moderated by CHHD Trainees Committee)	
9:55-10:50	(8min talk, 4min Q&A, 2min transition to next speaker)
9:55-10:07	**Dr. Adriano Cattani** (Neurosurgery Fellow, Dr. Roy Dudley Lab)
10:09-10:21	**Isabella Iasenza** (PhD Student, Dr. Kolja Eppert Lab)
10:22-10:35	**Dr. Lata Adnani** (Post-Doctoral Fellow, Dr. Janusz Rak Lab)
10:37-10:49	**Lingxiao Chen** (PhD Student, Dr. Nancy Braverman Lab)
Coffee Break	
10:50-11:00	
Morning poster presentations sessions	
11:00-12:35	Posters 9 - 28, 47 - 54
Lunch Break	
12:35-13:35	Individualized boxes to be picked up outside the auditorium
Keynote speaker presentation (Virtual via Zoom)	
13:40-14:30	**Dr. Melanie Barwick**, Hospital for Sick Children (Sickkids), Toronto
Title	Dissemination and Implementation Research and Practice - Key Considerations for Optimal Impact
Junior Oral Presentations Sessions (Moderated by CHHD Trainees Committee)	
14:35-15:30	(8min talk, 4min Q&A, 2min transition to next speaker)
14:35-14:47	Gabriela Regalado (Medical Student, Dr. Indra Gupta Lab)
14:49-15:01	Marissa Fazio (MSc Student, Dr. Marc Beltempo Lab)
15:03-15:15	Neeti Jain (MSc Student, Dr. Geneviève Bernard Lab)
15:17-15:29	Prachi Patel (Research Trainee, Dr. Dan Poenaru Lab)
CHHD Principal Investigator presentation	
15:30-16:00	Dr. Tina Montreuil, CHHD Scientist
Title:	Parental Mental Health during Pregnancy and the Sustained Effects on Child Development across the Lifespan
Afternoon Poster Presentations Sessions	
16:00-17:00	Posters 29 - 46
Coffee Break	
17:00-17:10	
Announcement of winners and closing remarks	
17:10-17:20	Dr. Meranda Nakhla, CHHD Associate Program Leader



Health and Safety Instructions

First and foremost, **if you are feeling sick, please stay at home!**

Throughout the day, we kindly ask the audience to remain spread out and avoid small clusters, and above all keep your masks on unless you are eating or sitting 2m away from everyone else. Our health is our responsibility and we have to be diligent to make this day a success.

Rules for the auditorium (room ES1.1129):

- Maximum capacity is 100 attendees with masks on at all times.
- No food or beverage permitted at any time at risk of being fined. The only permitted item is a capped bottle of water (while inside the auditorium).
- We kindly ask participants to treat the auditorium with courtesy as to not leave any messes behind.
- Any damage to the equipment or space of the auditorium will be charged to the individual causing the damage.

Rules for the space outside the auditorium (including the atrium of Bloc E):

- During poster presentations, both presenter and audience should be wearing masks.
- Masks can be removed temporarily to drink water.

Rules for food and drink:

- When snacks and hot beverages are provided, people are expected to be 2 meters apart since the masks will be off in the atrium.
- During lunch, participants are asked to practice the usual safety measures when having their lunch (lunch will be provided and individually packaged).

Please remember to enjoy your time and make the best out of it, but please don't forget that we are still required to practice safety measures because of the ongoing COVID-19 situation.

Awards

Best junior oral presentation:
$250

Best senior oral presentation:
$250

Junior poster presentations:

First place award: **$250**

Second place award: **$175**

Third place award: **$100**

Senior posters presentation:

First place award: **$250**

Second place award: **$175**

Third place award: **$100**

The term "Junior" refers to:
Medical student, Undergraduate student, MSc student

The term "Senior" refers to:
PhD student, Post-Doc, Research/Medical fellow

Only poster and oral presentations by trainees will be considered for awards.

Good luck to all the presenters!

Important Information for the Day

Gathering and setting up posters starts at 8:30 a.m. in the morning, but we encourage **morning** poster presenters to be there before 8:30 a.m. (research day committee members will be present starting 8:00 a.m.) to make sure everything runs smoothly and on time. **Afternoon** poster presenters can hang their posters during lunch time.

At 9:00 am sharp, Dr. Dufort will deliver the opening remarks and CHHD updates, so it is crucial that everyone is at the auditorium and seated so we minimize noise and interruption.

You will notice that we are adding a few minutes before every section of the schedule where applicable to accommodate for delays and/or technical surprises. But, rest assured, we are taking every measure to ensure that we respect the allocated times, and the research day follows the schedule in a smooth flow, and we count on you to make it a success.

QR code for the Zoom link for virtual attendees:

Please **scan** this QR code with your phone so you can go to the oral components of the research day (Student presentations/PI presentations/Keynote Speaker presentation)

Throughout the day you can reach out to any research day committee member if you have any questions or concerns and we will be ready and happy to assist in any way we can.

The research day committee members are:

Martin Karam, CHHD Program Manager

Atefeh Masoumipour, CHHD Technical Coordinator

Steven Serafini, CHHD Trainees Committee president
Sayaka Hansen, CHHD Trainees Committee co-VP of events
Elaine Lee, CHHD Trainees Committee co-VP of events
Yanchen Dong, CHHD Trainees Committee VP of communications
Diego Loggia, CHHD Trainees Committee VP of Finance
Neha Kamath, CHHD Trainees Committee VP of administration

Rosanna Camarda, CHHD Administrative Assistant

Abstracts

Abstracts selected for **morning oral presentations** session (Seniors Category)

1-4

Abstracts selected for **afternoon oral presentations** session (Juniors Category)

5-8

Abstracts selected for **morning poster presentations** session

9-28, 47-54

Abstracts selected for **afternoon poster presentations** session

29-46

Remark1: Titles have been removed from authorship line for space and organizational purposes and we apologize in advance if this causes any inconvenience or discomfort.

Remark2: Affiliations that were provided by presenters were added to the abstracts.

1- An *ex-vivo* model to study fast ripple high-frequency oscillations detected by SEEG using dedicated surgical specimens from pediatric focal epilepsy patients.

Cattani, A[1], Wang, S[2], Levesque, M[2], Atkinson, J[1], Farmer, JP[1], Avoli, M[2,3], Dudley, RWR[1]

Neurosurgery Fellow-Senior

Objective

High-frequency oscillations (HFOs, 80-500 Hz), specifically fast ripples (FRs, >250Hz), are recorded from ictogenic brain areas and are commonly observed in pediatric patients with drug-resistant epilepsy during stereoelectroencephalography (SEEG) evaluation. Detection of FRs helps to delineate the seizure onset zone for surgical resection increasing seizure freedom rates. Here, we investigate single neuron activity from dedicated pediatric epilepsy surgery specimens containing FRs during pre-surgical evaluation in order to establish an ex vivo model to study these important electrophyiological biomarkers toward a better understand of their epileptogenesis and potential pharmacological treatment.

Methods

Electrophysiological recordings were performed in acute slices from pediatric epilepsy surgery specimens containing high FRs rates (> 6 per minute), as detected by pre-surgical SEEG evaluation. Cell attached and whole-cell patch clamp recordings in voltage and/or- current-clamp modes were obtained from neurons located in cortical layers II to V. Spontaneous excitatory post-synaptic currents (sEPSCs) and ictal seizures-like events (SLEs) were analyzed.

Results

Twenty-five cells were recorded from 62 slices obtained from 6 patients. Thirteen spontaneous SLEs were recorded and high frequency of sEPSCs were identified in 8 neurons within the FRs resection areas. Pharmacology showed strong AMPA and Kainate component in cells recorded within FRs areas since most of EPSCs were blocked by NBQX.

Conclusion

Surgical specimens taken from areas of SEEG-detected FRs can be used as an ex vivo model to study FRs and to assess the impact of pharmacological interventions on these epileptogenic pertubations. This may allow for new insights aiming glutamate in the treatment of pharmaco-resistant epilepsy in pediatric patients.

2- High-throughput screen on primary human acute myeloid leukemia stem cells (LSCs) identifies novel anti-LSC compounds

Isabella Angela Iasenza[1,2], Safia Safa[3], Frédéric Barabé[4,5], Sonia Cellot[6], Brian T. Wilhelm[3], Kolja Eppert[2,7].

[1] Department of Medicine, McGill University, Montreal, QC, Canada.
[2] Division of Experimental Medicine, Research Institute of the McGill University Health Centre, Montreal, QC, Canada.
[3] IRIC-University of Montreal, Montreal, QC, Canada.
[4] Hôpital de l'Enfant-Jésus, Division of Hematology and Medical Oncology, CHU de Québec - Université Laval, Québec, QC, Canada.
[5] Hôpital de l'Enfant-Jésus, Québec, QC, Canada.
[6] Department of Pediatric Hematology Oncology, Sainte-Justine University Health Center, Montreal, Canada.
[7] Department of Pediatrics, McGill University, Montreal, QC, Canada.

PhD Student-Senior

Acute myeloid leukemia (AML) is an aggressive form of blood cancer that occurs in adults and children. Despite the use of cytotoxic standard-of-care drugs, patients often succumb to the disease partially due to the chemo-resistant nature of leukemic stem cells (LSCs). Hence, novel therapies targeting the unique biology of LSCs are needed.

High-throughput screens of human AML LSCs are generally not performed due to technical issues such as low LSC frequency within primary samples, an inability to purify LSCs, and the difficulty maintaining and expanding primary patient samples and LSCs in vitro. To overcome these challenges, we first optimized the conditions for a 4-week in vitro large-scale expansion (>600 million bulk) and enrichment of the CD34+ LSC-containing fraction (>90% purity) for a primary human AML sample (OCI-AML-8227). Next, we performed a high-throughput screen of 11,140 chemical molecules in 3 stages. First, the viability after treatment of OCI-AML-8227 CD34+ cells and healthy cord blood (CB) CD34+ cells was read out using a CellTiter Glo assay. 61 compounds had >70% inhibition of OCI-AML-8227 CD34+ cells and <30% inhibition on CB CD34+ cells. Next, we determined the dose response of each compound and refined the hits to 33 potent compounds with LC50 < 1 µM, including novel compounds and classes previously shown to target bulk and leukemic stem cells in AML. Finally, we determined the LC50 specifically in the CD34- (blast) and CD34+CD38- (LSC-enriched) OCI-AML-8227 populations using flow cytometry. We identified 25 novel anti-LSC compounds with high efficacy against CD34+CD38- AML cells. The top 3 compounds with known targets were validated in a second LSC-enriched model with poor prognosis, OCI-AML-20, and confirmed anti-LSC activity. We now aim to examine LSC eradication in a panel of genetically defined primary AMLs to be able to determine the broad applicability of these compounds.

3- Angiocrine extracellular vesicles impose mesenchymal reprogramming upon proneural glioma stem cells

Lata Adnani[1], Jordan Kassouf[2], Brian Meehan[1], Cristiana Spinelli[1], Nadim Tawil[1], Ichiro Nakano[3], Janusz Rak[1,4]

[1] Research Institute of the McGill University Health Centre, Montreal, QC, H4A 3J1, Canada.
[2] Department of Biochemistry, McGill University, Montreal, QC, H4A 3J1, Canada.
[3] Department of Neurosurgery, Hokuto Social Medical Corporation, Hokuto Hospital, Kisen-7-5 Inadacho, Obihiro, Hokkaido, 080-0833, Japan.
[4] Department of Pediatrics, McGill University, Montreal, QC, H4A 3J1, Canada.

Post-Doctoral Fellow-Senior

Glioblastoma (GBM) is an incurable form of primary astrocytic brain tumor driven by glioma stem cell (GSC) compartment closely associated with the vascular niche. GSC phenotypes are heterogeneous and range from proneural to mesenchymal-like, the latter characterised by greater invasiveness. Here we document the secretory (angiocrine) role of endothelial cells and their derived extracellular vesicles (EVs) as drivers of proneural-to-mesenchymal reprogramming of GSCs. These changes involve activation of matrix metalloproteinases (MMPs) and NFκB, and inactivation of NOTCH, while altering responsiveness to chemotherapy and driving infiltrative growth in the brain. Our findings suggest that EV-mediated angiocrine interactions impact the nature of cellular stemness in GBM with implications for disease biology and therapy.

4- Systemic Lipid Deficiency and Liver Pathophysiology in Pex1-G844D mice

Lingxiao Chen, Catherine Argyriou, Erminia Di Pietro, Hong Choi, Caroline Daneault, Daniel Charpentier, Esther Nuebel and Nancy Braverman

PhD Student-Senior

Zellweger Spectrum disorder (ZSD) is a multi-system disorder caused by mutations in any of 13 PEX genes, leading to defects in peroxisome assembly and function. Peroxisomes are abundant in liver, where they are required for the maintenance of lipid homeostasis throughout the body. Recently, systemic deficiency of fatty acids (FA) and their derivatives were reported in ZSD patients. As FAs are essential nutrients, signalling molecules, and building blocks of cellular membranes, we considered lipid deficiency, stemming from hepatic synthesis defects, as a potential contributor to failure to thrive and multi-systemic defects in ZSD. We investigate this in Pex1-G844D mice, which carry the murine equivalent of the common human PEX1-G843D mutation.

Pex1-G844D homozygous mice had growth restriction and hepatomegaly. They showed abnormal liver phenotypes which progressed to fibrosis and cancer, recapitulating liver disease in patients. They had hypoglycaemia, hypotriglyceridemia and hypoinsulinemia. We propose that hypotriglyceridemia drives consumption of glucose stores, resulting in hypoglycaemia, sustaining low insulin level, and reduced hepatic FA synthesis. In support of this hypothesis, Pex1-G844D mice had downregulation of lipogenesis and carbohydrate catabolism, upregulation of FA oxidation and hepatic FA uptake on qPCR and immunoblot analyses. They also had an abnormal hepatic lipid profile with accumulation of storage lipids and reduced membrane lipids in contrast to total lipid deficiency in serum. There was reduced membrane FA derivatives in both tissues evaluated. Serum lipoprotein analysis revealed a reduction of non-HDL triglycerides, implicating a reduction of hepatic VLDL-triglyceride secretion. An increased content of serum non-HDL cholesterol suggested dysregulation of cholesterol metabolism.
In summary, we found that reduced biosynthesis of FA derivatives and dysregulated lipid transport underlies systemic FA deficiency and hepatosteatosis in Pex1-G844D mice. This

pathway analysis enhances our understanding of ZSD pathogenesis and provides us with novel therapeutic strategies to pharmacologically upregulate hepatic fatty acid synthesis.

5- The effect of arsenic exposure on mouse nephrogenesis

Gabriela Regalado[1], Carlos Agustín Isidro Alonso[2], Ajay Rajaram[3], Pierre-Olivier Fiset[3], Koren Mann[4], Aimee K. Ryan[2,5,6], Indra Gupta[2,5,6]

[1] Faculty of Medicine and Health Sciences, McGill University, Montreal, Quebec, Canada
[2] The Research Institute of the McGill University Health Centre, Montreal, Quebec, Canada.
[3] Department of Pathology, McGill University Health Centre, Montreal, QC, Canada.
[4] Department of Medicine, Jewish General Hospital, McGill University, Montreal, Quebec, Canada.
[5] Department of Human Genetics, McGill University, Montreal, Quebec, Canada.
[6] Department of Pediatrics, McGill University, Montreal, Quebec, Canada.

Medical Student-Junior

Arsenic is a naturally occurring toxicant that is teratogenic in animal models. Millions of people are exposed to high arsenic concentrations (50-800ppb). Previous work has identified gestation as an important window for arsenic exposure. Given the increased prevalence of chronic kidney disease, we sought to determine if there is an effect on nephrogenesis. We also aim to evaluate the use of an artificial intelligence (AI) model to increase the feasibility of nephron counts in the future.

C57BL/6J pregnant mice were exposed to tap water or 200 ppb arsenic water at embryonic day 0.5. Pups were euthanized 2 weeks postnatally. Right kidneys were paraffin-embedded, sectioned at 7 µm thickness and stained with hematoxylin and eosin. 10% of each kidney was sampled by choosing sections 70 µm apart to avoid double counting. Eight whole slide images (WSIs) were manually annotated for an initial cycle of training of the neural network for glomeruli identification, which was used as a proxy for nephron number(NN). A second cycle of training was conducted using 15 WSIs. NN was calculated using the predicted glomeruli number and a validated formula.

Pups in the arsenic group had lower body weight than those in the control group ($p=0.02$). The AI model achieved a mean intersection of union of 80.02% after two cycles of training. Mean NN for the control group was 24884 ±2783 nephrons and 23314 ±3427 nephrons for the arsenic group: 6.7% fewer than control ($n=25$ kidneys/group). The decrease was not statistically significant using an unpaired t-test ($p=0.11$).

Employment of an AI model appears to be appropriate to increase the efficiency of NN studies. While there was no statistical between both groups, preliminary data suggests that arsenic exposure may impair nephrogenesis. Future work will expand the sample size.

6- The association of occupancy, nursing overtime, and nurse provision ratios with the risk of nosocomial infection in the neonatal intensive care unit

Marissa Fazio[1], Elias Jabbour[1], Valérie Bertelle[4], Anie Lapointe[3], Guy Lacroix[2], Sophie Gravel[5], Michèle Cabot[6], Bruno Piedboeuf[2], Marc Beltempo[1]

* A list of Network Member Investigators is presented in the Acknowledgments.
[1] McGill University, Montreal, QC, Canada
[2] Université Laval, Quebec, QC, Canada
[3] Université de Montréal, Montreal, QC, Canada
[4] Université de Sherbrooke, Sherbrooke, QC, Canada
[5] Division of neonatology, CHU Sainte-Justine, Montreal, QC, Canada
[6] Division of neonatology, CHU de Québec, Québec, QC, Canada.

MSc Student-Junior

Background: Very preterm infants (<33 weeks gestational age) admitted to the Neonatal Intensive Care Unit (NICU) are at a high risk of developing a nosocomial infection (NI). NICU organizational factors may contribute to the risk of infection.

Objective: To evaluate the association of unit occupancy, nursing overtime, and nursing provision ratios with the risk of NI among very preterm infants.

Methods: Retrospective cohort design of infants born <33 weeks admitted to 3 tertiary-level NICUs in Québec between 2014–2018. Infant data was obtained from the Canadian Neonatal Network database and linked to unit administrative data. Organizational variables were unit occupancy rate, nursing overtime ratio (OTR, overtime hours/total hours worked), and nursing provision ratio (NPR, available/recommended nurses). Mean values of the organizational variables during the 3-day period before NI (confirmed by positive blood and/or cerebrospinal fluid culture taken >72 hours after birth) were compared to the 3 days before discharge or days 42-45 (if discharged after day 45) for infants without NI. Associations were assessed using mixed-effect logistic regression models adjusted for patient characteristic risk factors and site (the random-effect).

Results: A total of 238/2046 (11.6%) infants developed NI and the median time to infection was 11 days (IQR [7,21]). Median unit occupancy was 89.1% (IQR [81.7%, 94.7%]), median OTR was 4.7% (IQR [2.4%, 7.3%]) and median NPR was 101.2% (IQR [86.4%, 126.3%]). Unit occupancy and NPR were not associated with NI (adjusted Odds Ratio (aOR); 0.99, 95% CI [0.97–1.02] and 0.99 [0.97–1.00], respectively). The OTR was associated with the odds of NI (aOR;1.10, 95% CI [1.05–1.14]). Sensitivity analysis using different reference periods (days 8-11 and days 18-21 for infants without NI) also yielded similar results.

Conclusion: Nursing overtime is associated with increased infection risk among very preterm infants in the NICU.

7- Evaluating the pathophysiological mechanisms underlying the neuronal defects seen in patients with severe POLR3-HLD

Neeti Jain[1,2], Stefanie Perrier[1,2], Alexandra Chapleau[1,2], Julia Macintosh[1,2], Chia-Lun Wu[2], Geneviève Bernard[1,2,3,4]

[1] Integrated Program in Neuroscience, McGill University, Montreal, Canada.
[2] Child Health and Human Development Program, Research Institute of the McGill University Health Centre, Montreal, Canada.
[3] Department of Neurology and Neurosurgery, McGill University, Montreal, Canada.
[4] Department of Pediatrics and Human Genetics, McGill University, Montreal, Canada.

MSc Student-Junior

Hypomyelinating leukodystrophies are a group of rare inherited white matter disorders characterized by abnormal myelin deposition during development. RNA polymerase III-related hypomyelinating leukodystrophy (POLR3-HLD) is caused by biallelic pathogenic variants in genes encoding RNA polymerase III (Pol III) subunits, including POLR3A. Pol III is responsible for the transcription of small non-coding RNAs with important roles in gene expression and protein synthesis. POLR3-HLD has a wide phenotypic spectrum, ranging from mild to typical and severe forms of the disease. On the severe end of the spectrum, some patients harbour a specific genotype with compound heterozygous biallelic pathogenic variants in POLR3A, including one allele containing a variant causing a premature stop codon, and the other allele contains the c.1771-7C>G intronic splicing variant. In our past studies, neuropathological investigations on patients with a severe presentation showed neuronal abnormalities with progressive involvement of the striatum (i.e., putamen and caudate), and thalamus. Therefore, we hypothesize that the splicing variant causes a primarily neuronal disease with cell-specific defects involving neurons in the basal ganglia. The overarching objective of this study is to evaluate the pathophysiological mechanisms underlying the neuronal defects seen in patient with severe POLR3-HLD. This will involve studying the phenotype in vitro using iPSCs to generate cortical neural progenitor cells (NPCs) and collecting tissue samples from three severe patients in the striatum, cerebral white matter, cortex and cerebellum. Once RNA is extracted from these samples, Pol III target levels will be evaluated. This project aims to better understand the relationship between the specific genotype and atypical phenotype seen in POLR3-HLD severe patients and examine potential differences in Pol III function in POLR3-HLD severe patient NPCs and brain tissue. Evaluation of this will shed light on the disease pathophysiology and open the door for the development of potential therapeutics for this devastating neurodegenerative disease.

8- Patient Experience or Patient Satisfaction? - A Systematic Review of Child- and Family-Reported Experience Measures in Pediatric Surgery

Julia Ferreira[1,2], Prachikumari Patel[2], Elena Guadagno[2], Nikki Ow[3], Jo Wray[4], Sherif Emil[1,2], Dan Poenaru[1,2].

[1] McGill University Faculty of Medicine and Health Sciences
[2] Harvey E. Beardmore Division of Pediatric Surgery, The Montreal Children's Hospital, McGill University Health Center, Montreal, Quebec, Canada
[3] Department of Occupational Science and Occupational Therapy, Faculty of Medicine, The University of British Columbia, Vancouver, British Columbia, Canada
[4] Great Ormond Street Hospital for Children NHS Foundation Trust, London, UK

Research Trainee-Junior

Purpose
Patient-reported outcomes measures (PROMs) and patient-reported experience measures (PREMs) are increasingly recognized as important health care quality indicators. PREMs measure patients' perception of the care they have received, differing from satisfaction ratings, which measure their expectations. The use of PREMs in pediatric surgery is limited, prompting this systematic review to assess their characteristics and identify areas for improvement.

Methods
A search was conducted in eight databases from inception until January 12, 2022, to identify PREMs used with pediatric surgical patients, with no language restrictions. We focused on studies of patient experience but also included studies that assessed satisfaction and sampled experience domains. The quality of the included studies was appraised using the Mixed Methods Appraisal Tool.

Results
Following title and abstract screening of 2,633 studies, 51 were included for full-text review, of which 22 were subsequently excluded because they measured only patient satisfaction rather than experience, and 14 were excluded for a range of other reasons. Out of the 15 included studies, questionnaires used in 12 studies were proxy-reported by parents and in 3 by both parents and children; none focused only on the child. Most instruments were developed in-house for each specific study, without patients' involvement in the process, and were not validated.

Conclusions
Although PROMs are increasingly used in pediatric surgery, PREMs are not yet in use, being typically substituted by satisfaction surveys. Significant efforts are needed to develop and implement PREMs in pediatric surgical care, in order to effectively capture children's and families' voices.

9- Factors for Coping with the COVID-19 Pandemic: Contextualizing Experiences of Canadian Caregivers of Youth with Developmental Delays and Disabilities

Anna Katalifos[1], Afiqah Yusuf[1,2], Sakiko Yamaguchi[3], Keiko Shikako[3], Mayada Elsabbagh[1,2]

[1] Department of Neurology and Neurosurgery, McGill University
[2] Azrieli Centre for Autism Research, Montreal Neurological Institute-Hospital, McGill University
[3] School of Physical and Occupational Therapy, McGill University

MSc Student-Junior

The UNICEF-World Health Organization Global Report on Developmental Delays, Disorders, and Disabilities (DDDs) caregiver survey found that half of youths with DDDs and their caregivers struggled to cope during the pandemic. Governments created service strategies supporting vulnerable groups. Little is known about the alignment between COVID-19 policies for persons with disabilities and their lived experiences. Contextualizing caregivers' experiences can promote the development of public supports exiting the pandemic. We aimed to contextualize experiences of youth with DDDs and their caregivers during the pandemic in relation to Canadian COVID-19 policies for persons with disabilities. Online survey data were collected from June-July 2020, leading to a pan-Canadian convenience sample of caregivers of youth with DDDs (N=883). Participants were asked to write down anything making it harder and easier to cope during the pandemic. We conducted a thematic analysis of responses using inductive and deductive coding on NVivo software. Overarching codes were mapped onto federal and provincial COVID-19 policies. Parallels with policies supported exploring of families' experiences during the pandemic. Five hundred and thirty-one (N=531) participants answered open-ended questions. Individual barriers to coping were mental health complications, concerns about the child's condition regressing, online schooling challenges, insufficient play spaces, and physical health management. Environmental barriers included worsening family finances, loss of services, and stigma. In contrast, media entertainment, family time, outdoor spaces, and the child's resilience were facilitators. Environmental facilitators were community support, information from government, and telehealth service access. Few COVID-19 policies aligned practical services to caregiver-identified barriers. Facilitators aligned with pre-existing policies, but some COVID-19 restrictions were deterrents to accessing these facilitators during the pandemic. Prioritizing needs of families of youths with DDDs during public health emergencies can impact their wellbeing. Increasing financial benefits for these families, offering telehealth services, and creating inclusive play spaces are priority areas exiting the pandemic.

10- Design and implementation of a gamified mobile application for youth with disabilities: A user-centered design approach

Ebrahim Mahmoudi, Carlos Denner, Annette Majnemer, Mehrnoosh Movahed, Keiko Shikako

MSc Student-Junior

Introduction:
Leisure participation is an essential component of youth's life, however, youth with disabilities (YWD) experience limitations in participation and involvement in activities compared to typically developing peers. Despite the abundance of research investigating different interventions to enhance the participation of YWD in leisure activities, there are substantial gaps in how to successfully implement their findings, limiting the impact of research on public health outcomes. Innovative technological advances that facilitate knowledge sharing, such as mobile applications could significantly improve the health and well-being of marginalized groups.

Objectives:
This study aims to design and implement a gamified mobile application based on the YWD's needs and preferences to enhance their participation in leisure activities.

Methods:
This study will be a mixed method-sequential exploratory design in three phases. Phase 1 will be an interpretive description qualitative by conducting in-depth semi-structured interviews with a YWD 14-24 years old and their parents (n=20). Phase 2 consists of multiple participatory design sessions on Zoom with participants and technology experts to identify the most enjoyable and feasible gamification elements to implement in the app. To evaluate the implementation of the gamification features, phase 3 will be an interrupted time-series design over eight weeks to measure the feasibility outcomes, including recruitment rates, retention, gamification features usage and usability of application and participants' satisfaction outcomes.

Anticipated Results:
This study will evidence the pathways for the development of user-centered design in the mobile-health domain for vulnerable populations through the creation of technological tools that respond to YWD's preferences and user-centered design standards. The findings of this study will contribute to enhancing mobile health solutions that benefit Canadian YWD so they may participate in leisure activities of their choosing, support their inclusion in the community, and develop equity as proposed by the United Nations Sustainable Development Goals (goal 10) and CRPD.

11- Use of Machine Learning in Pediatric Surgical Clinical Prediction Tools: A Systematic Review

Amanda Bianco[1], Zaid A.M. Al-Azzawi[1], Elena Guadagno[2], Esli Osmanlliu[4], Jocelyn Gravel[3], Dan Poenaru[1,2]

[1]Faculty of Medicine and Health Sciences, McGill University, Montreal, Quebec, Canada
[2]Harvey E. Beardmore Division of Pediatric Surgery, The Montreal Children's Hospital, McGill University Health Centre, Montreal, Quebec, Canada
[3]Department of Pediatric Emergency Medicine, Sainte-Justine Hospital, Université de Montréal, Montreal, Quebec, Canada
[4]Department of Pediatrics, McGill University Health Centre, Montreal, Quebec, Canada

Medical Student-Junior

Purpose: Clinical prediction tools (CPTs) are decision-making instruments utilizing patient data to predict specific clinical outcomes, risk-stratify patients, or suggest personalized diagnostic or therapeutic options. Recent advancements in artificial intelligence have resulted in a proliferation of CPTs created using machine learning (ML) - yet the clinical applicability of ML-based CPTs and their validation in clinical settings remain unclear. This systematic review aims to compare the validity and clinical efficacy of ML-based to traditional CPTs in pediatric surgery.

Methods: Nine databases were searched from 2000 until July 9, 2021 to retrieve articles reporting on CPTs and ML for pediatric surgical conditions. PRISMA standards were followed, and screening was performed by two independent reviewers in Rayyan, with a third reviewer resolving conflicts. Risk of bias was assessed using the PROBAST.

Results: Out of 8,300 studies, 48 met the inclusion criteria. The most represented surgical specialties were pediatric general (14), neurosurgery (13) and cardiac surgery (12). Prognostic (26) CPTs were the most represented type of surgical pediatric CPTs followed by diagnostic (10), interventional (9), and risk stratifying (2). One study included a CPT for diagnostic, interventional and prognostic purposes. 81% of studies compared their CPT to ML-based CPTs, statistical CPTs, or the unaided clinician, but lacked external validation and/or evidence of clinical implementation.

Conclusions: While most studies claim significant potential improvements by incorporating ML-based CPTs in pediatric surgical decision-making, both external validation and clinical application remains limited. Further studies must focus on validating existing instruments or developing validated tools, and incorporating them in the clinical workflow.

12- Sphingosine and Ceramide Regulate Acquisition of Fertilizing Ability in Human Spermatozoa

Steven Serafini, Christian O'Flaherty

MSc Student-Junior

1 in 6 couples today in Canada struggle with infertility. 50% of these cases are due to a male-related factor, of which 34% are cases of idiopathic infertility. Assisted reproductive techniques (ARTs) (e.g., IVF and ICSI) are a few of the infertility treatments. However, these techniques are costly (15-30K per cycle), have low efficiency (~30%), and are linked to developmental, cognitive, and fertility issues in the offspring. Semen analysis, the sole means of assessing male infertility, does not assess essential functions like capacitation. Capacitation encompasses biochemical and morphological adaptations, including low levels of reactive oxygen species (e.g., ROS) and protein phosphorylation, allowing the spermatozoon to acquire fertilizing ability. The role of lipid signalling in capacitation is largely unknown. Sphingosine (Sph), ceramide (Cer), and their phosphorylated forms S1P and C1P promote nitric oxide (NO□) production in endothelial cells and macrophages. We determined whether Sph, Cer, S1P and C1P and the S1P signalling promote capacitation, triggering tyrosine (P-Tyr) and PI3K (P-PI3K) phosphorylations. Human spermatozoa were incubated with fetal cord serum ultrafiltrate (FCSu, capacitation inducer), Sph, or Cer, with or without inhibitors of SphK1 and CERK, kinases that produce S1P and C1P, respectively, inhibitors of the S1P receptor 1 (SP1PR1), or ceramidase (that converts Cer into Sph) at 37°C for 4h. Tyrosine phosphorylation (P-Tyr) and phospho-PI3K (P-PI3K) levels were determined by immunoblotting. The localization of S1P1R and phospho-SphK1 (P-SPHK1) in spermatozoa was determined by immunocytochemistry. Sph and Cer increased P-Tyr compared to non-treated controls. SPHK1 and CERK inhibition decreased P-Tyr and P-PI3K in capacitated spermatozoa compared to controls. S1PR1 and P-SPHK1 were localized in the sperm post-acrosomal region. P-SPHK1 intensity increased during capacitation. Inhibition of S1PR1 decreased P-Tyr and P-PI3K during capacitation. S1P signalling is necessary to activate PI3K during capacitation, and its dysfunction could cause male infertility. Supported by CIHR (PJT-165962).

13- Characterizing the Regulation of Maternal NODAL Expression in the Uterus During the Peri-Implantation Period

Elaine Lee[1,2], Craig B. Park[1,2], Daniel Dufort[1,2,3]

[1] Department of Experimental Medicine, McGill University, Montréal, Canada
[2] Child Health and Human Development Program, Research Institute of the McGill University Health Centre, Montréal, Canada
[3] Department of Obstetrics and Gynecology, McGill University, Montréal, Canada

MSc Student-Junior

The Nodal protein (NODAL) is a member of the transforming growth factor-beta superfamily with a well-defined role in embryonic development. Recently, interest in the role of Nodal in female reproduction and pregnancy has increased. Using mice with a uterine-specific knockout of the Nodal gene, we demonstrated that aberrant Nodal signaling precipitated phenotypic features reminiscent of pregnancy complications, such as reduced implantation and fecundity. This indicated that NODAL may play a critical role in early pregnancy. Despite this, the regulation of its expression remains unknown. We previously discovered that NODAL is not expressed in mice uteri prior to mating, which suggests that an early reproductive event, such as mating or fertilization, may be involved in its activation. Similar expression patterns in female mice bred with vasectomized males further indicates that mating activates uterine NODAL expression. This project aims to identify how different parameters of mating affect uterine NODAL expression during peri-implantation. To study if uterine NODAL expression changes due to the mechanical stress of mating, we will use immunoblotting to measure NODAL levels in female mice that will be intravaginally injected with a buffer solution to simulate the mechanical stress of copulation. To investigate the effect of paternal factors, we will use immunoblotting to analyze NODAL expression in females exposed to fluids from male reproductive glands. Because of its association with numerous pregnancy complications, we hope that characterizing how NODAL expression is regulated can ultimately enhance the field of perinatology by identifying new therapeutic targets and expanding knowledge on mammalian reproduction.

14- Role of citrate and ATP-citrate lyase in human sperm capacitation

Diego Loggia, Cristian O'Flaherty

MSc Student-Junior

Infertility is rising worldwide; couples that struggle with infertility increased from 8% in the 1980s to almost 17% today in Canada. The cause of half these cases can be traced to men, of which 30% suffer from idiopathic infertility. Thus, there is an unmet need to characterize the mechanisms underlying male infertility.

Citrate is an abundant energy metabolite in human spermatozoa that has been reported to be deficient in the seminal plasma of idiopathic infertile men and in the follicular fluid of infertile women, which normally promote the process of capacitation. Capacitation involves a series of biochemical changes which allow the spermatozoon to recognize and fertilize the oocyte. Human sperm capacitation is associated with production of low levels of reactive oxygen species, such as nitric oxide (NO•), protein phosphorylation and acetylation. However, the role of citrate in human sperm capacitation is unknown. We hypothesize that citrate is required for intracellular NO• production and protein acetylation to drive sperm capacitation. Our objectives are to determine 1) whether citrate supports sperm capacitation, 2) whether the cytosolic ATP-citrate lyase (ACLY) and mitochondrial citrate transport protein (CTP) are involved in capacitation, 3) the levels of NO• and protein acetylation in spermatozoa capacitated in citrate-supplemented medium with or without ACLY inhibition.

We found that human spermatozoa, incubated with 10 mM citrate and fetal cord serum ultrafiltrate (a capacitation inducer), capacitated in BWW medium without any other energy substrates. In addition, ACLY inhibition prevented FCSu-induced capacitation. These results demonstrate that citrate and ACLY are needed for capacitation. Studies are ongoing to determine whether citrate/ACLY and CTP promote protein acetylation and NO production during capacitation. These studies will help to understand citrate regulation in sperm capacitation in the context of reactive oxygen species and protein acetylation, and will help ameliorate treatment strategies for male infertility.

15- Elucidating the mechanism of the anti-inflammatory effect of Nodal on macrophages stimulated by LPS

Rose-Andrea Corneli[1,2], Taghreed Ayash[1,2], Daniel Dufort[1,2,3]

[1] Department of Experimental Medicine, McGill University, Montréal, Canada
[2] Child Health and Human Development Program, Research Institute of the McGill University Health Centre, Montréal, Canada
[3] Department of Obstetrics and Gynecology, McGill University, Montréal, Canada

MSc Student-Junior

NODAL, a secreted factor of the Transforming Growth factor Beta family (TGF-ß), plays an important role in embryo development. In the mouse uterus, NODAL is expressed shortly after mating. Its tissue specific deletion has been linked to decreased fertility in our mouse model. Conversely, loss of one of both alleles of NODAL in mice has been shown to predispose the uterus to an early onset of the inflammatory state via an elevation of the basal level of proinflammatory cytokines on day 16.5 of gestation. This precocious induction of the proinflammatory environment results in increased sensitivity to Lipopolysaccharide (LPS) and resulting preterm birth in our mouse model. Addition of LPS for 6 hours results in increased expression of several proinflammatory cytokines including IL-1□, IL-6, IL-12p, TNF-α, and IFN-γ. Pre-treatment of macrophages for 1 hour with Nodal significantly reduced the expression of these proinflammatory cytokines. Since LPS signals through the Toll-like-receptor 4 (TLR4), we have assayed whether pre-treatment of Nodal affects the downstream signaling pathway of TLR4. We assayed the effect of Nodal protein levels of TLR4, MYD88 and TRAF6. Pre-emptive results suggest rNodal pre-treatment followed by LPS did not protein level of TLR4, TRAF6 nor MYD88.

16- Right ventricular dominance predicts postnatal intervention requirement in those with fetal suspicion of coarctation of the aorta

Sam Amar[1], Shiran Sara Moore[1,2], Punnanee Wutthigate[3], Amanda Ohayon[1,4], Daniela Villegas Martinez[1], Jessica Simoneau[1], Claudia Renaud[5], Gabriel Altit[1,4]

[1]Division of Neonatology, Department of Pediatrics, McGill University Health Centre – Montreal Children's Hospital, Montreal, Quebec, Canada.
[2] Division of Neonatology, Dana Dwek Children's Hospital, Tel Aviv Medical Centre, Tel Aviv, Israel.
[3]Division of Neonatology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand.
[4]Department of Experimental Medicine, Department of Pediatrics, McGill University, Montreal, Quebec, Canada.
[5]Division of Pediatric Cardiology, Department of Pediatrics, McGill University Health Centre – Montreal Children's Hospital; Montreal, Quebec, Canada.
Corresponding Author: Gabriel Altit, MDCM, MSc, FRCPC, FAAP, Neonatology – Montreal Children's Hospital - McGill University; 1001 Decarie, Montreal, QC, Canada, H4A 3J1; gabriel.altit@mcgill.ca

Medical Student-Junior

Objectives: The fetal diagnosis of coarctation of the aorta (CoA) is currently associated with a high false-positive rate. We sought to establish a set of traditional and speckle-tracking fetal echocardiography markers predictive of true CoA in neonates with a prenatal suspicion.

Methods: Infants with a fetal echocardiography performed between October 2013 and May 2022 for an antenatal suspicion of CoA were included in this retrospective study. We compared the fetal ventricular and arch dimensions, as well as the deformation parameters, of infants who required a postnatal intervention for their CoA to those who did not (control group). Data extractors were masked to the outcome. The first fetal echocardiogram available was used.

Results: A total of 75 newborns were included, of which 59 (79%) had an aortic arch with non-significant obstruction upon ductal closure, and 16 (21%) underwent a neonatal intervention for a confirmed CoA. Compared to the controls, those with CoA had an increased right to left ventricular dominance. Indeed, they had an increased right to left ventricular end-diastolic area [RV/LV EDA] ratio in the apical view (1.21 [0.32] vs 1.63 [0.34]; $p<0.0001$). A decreased right ventricular peak longitudinal strain was observed in the CoA group (-20.95 [2.96] vs -18.56 [3.14] %, $p=0.006$). The RV/LV EDA ratio was the most sensitive predictor of CoA and identified all cases with CoA. Indeed, a cut-off >1.229 had a specificity of 66.1% and a sensitivity of 100% (receiver operating characteristic curve with an area under the curve of 0.84).

Conclusions: Right ventricular dominance, especially the right to left ventricular end-diastolic area ratio in the fetal apical 4-chamber view, is a useful tool to identify low-risk for a true CoA during fetal life.

17- Stress and Quality of Life of Parents with Children with 4H Leukodystrophy

Lentini L[1], Toutounchi H[1], Fournier S[1], Tran L[1], Chen X[1], Bernard G[1]

[1] Division of Medical Genetics, McGill University Health Centre; Departments of Neurology and Neurosurgery, Pediatrics and Human Genetics; Child Health and Human Development Program, Research Institute of the McGill University Health Centre, Montreal, Quebec, Canada

MSc Student-Junior

4H (hypomyelination, hypodontia and hypogonadotropic hypogonadism) leukodystrophy (LD) is a genetic disorder characterized by insufficient cerebral myelin deposition during development, typically in children, leading to progressive disability and premature death. While the disease has a tremendous impact on patients and their families, this has never been studied systematically. Few studies examine quality of life (QoL) of patients and parental stress of LDs, however none specifically investigate 4H. The goal of this project is to study the stress and QoL of parents of patients with 4H. We hypothesized that parental stress would be higher and QoL would be lower relative to parents of healthy children, and certain clinical features would influence these scores. Thus, questionnaires and clinical assessments were collected cross-sectionally. Questionnaires assessed parents' well-being, stress-impacting factors, perceptions of injustice, and coping mechanisms. Stress and QoL scores were compared to healthy populations using one-sample t-tests. Perceived injustice scores were compiled into percentile ranges. Correlations and chi-squares were used to define the relationship between clinical features and stress scores.

Parents of children with 4H had lower QoL compared to parents of healthy children, yet their stress mostly fell within the low stress percentiles. Mothers' stress and QoL scores were negatively correlated (Pearson r =-0.5676; $p<0.05$). Mothers' perceived injustice scores ranged from average to high, and fathers ranged from very low to very high. Helpful coping mechanisms included those where parents felt in control, and least helpful were those irrelevant to their child's care. Anarthria was one clinical feature found to contribute to parents' stress.

QoL and parental stress for parents with children with 4H was shown to be lower than parents of healthy children. Nonetheless, it is important to note other factors could be influencing these findings. Thus, additional data is required to decipher the association between clinical features and stress scores.

18- Whole-exome sequencing reveals several pathogenic variants in genes known to cause monogenic forms of diabetes

Alix Vanpoperinghe, Natalija Popovic, Angeliki Makri, Constantin Polychronakos

MSc Student-Junior

One of the most common chronic diseases of childhood is type 1 diabetes (T1D) which is due to the autoimmune destruction of insulin-producing pancreatic beta cells. However, there are a group of non-autoimmune monogenic forms of the disease, like maturity-onset diabetes of the young (MODY), which can lead to hyperglycemia, often misdiagnosed as T1D. Correct diagnosis is essential as some forms can be treated with oral medication instead of insulin. The current inheritance model is exclusively autosomal dominant and includes 14 validated MODY genes(OMIM #606391). in addition, rare cases of monogenic diabetes can be syndromic and/or neonatal. We hypothesize that non-syndromic, non-neonatal autosomal recessive forms of diabetes exist but have not been discovered because of lack of compelling family history.

Towards testing this hypothesis with our cross-Canada Accurate Diagnosis in Diabetes for Appropriate Management (ADDAM,clinical trial NCT03988764), we first searched for autoantibody-negative patients with a clinical diagnosis of T1D who carried mutations in the known MODY genes. Rare, protein-altering variants in 192 exomes were selected and classified according to the American College of Medical Genetics guidelines for evidence of pathogenicity. Here, we find 12 highly likelyoccurrences, including 3 ABCC8 variants (1 pathogenic, 2 warm VUS), 3 HNF1A variants (1 frameshift and 2 high-scoring missense), 2 GCK variants (high-scoring missense) and 5biallelic WFS1 variants (1 pathogenic frameshift + likely pathogenic deletion, 4 high-scoring missense), in patients with no evidence of Wolfram syndrome. This confirmation of the previously unsuspected non-syndromic diabetes caused by WFS1 variants is proof of principle for our postulation that searching for recessive forms of monogenic diabetes is worthwhile. Furthermore, this study has the potential to enhance the screening and diagnostic algorithms for young patients and their access to more targeted treatments. Improving this will be useful in efforts to limit patients that will proceed to genetic testing and develop new cost-effective standards of care for monogenic diabetes.

19- Elucidating the role of sphingolipids in the pathogenesis of hepatocellular adenoma linked to GSD Ia

Jae Yeon Park[b], Karine Bernier[b], Yeniay Erdem[b], Karen Christensen[b], Dwight D. Koeberl[c], Rima Rozen[b], Farah El Turk*[a,b], John J. Mitchell*[a,b]

[a] Department of Pediatrics, Montreal Children's Hospital
[b] Research Institute of McGill University Health Center
[c] Division of Medical Genetics, Department of Pediatrics, Duke University School of Medicine

MSc Student-Junior

Glycogen storage disease Ia (GSD Ia) is an inherited metabolic disorder characterized by severe hypoglycemia and accumulation of glycogen secondary to a deficiency of the glucose-6-phosphatase-α. With the introduction of cornstarch therapy, metabolic control in GSD Ia has dramatically improved. Nevertheless, long-term complications, such as hepatocellular adenomas (HCA) continue to occur in GSD Ia patients. The build-up of fat in the liver has been observed in both non-alcoholic fatty liver disease (NAFLD) and GSD Ia. If untreated, NAFLD can transform to HCA whose inflammatory pathways may also be observed in the aetiology of GSD Ia-HCA. Recent studies pointed out the 'sphingolipid turnover' as a hallmark of HCA. Hence, we hypothesize that sphingolipids play a major role in the inflammatory process that leads to the development of hepatic adenomas/carcinomas.

Using liquid chromatography-tandem mass spectrometry, we have analyzed 18 sphingolipids species in GSD Ia patients and animal models to examine if perturbations in sphingolipid metabolism are present. In both GSD Ia murine and human plasma, the concentrations of sphingolipids, particularly the ceramides, were significantly increased. Furthermore, the compositional analysis of total sphingolipid contents revealed a significant disruption in subclass distributions in GSD Ia. We compared the plasma versus liver sphingolipid profiles in GSD Ia mice to identify whether circulating sphingolipids can indicate the transition of liver metabolism. Preliminary data revealed that the pattern of alterations in liver sphingolipids is not identical to the plasma in mice model. We will further study on dissecting the relationship between plasma and liver sphingolipidome in GSD Ia mice model, where mice are obtained at different stages of the disease. In conclusion, our study highlights the perturbations of sphingolipid concentrations as well as the compositional alterations in GSD Ia, which would be a key concept in developing a new biomarker to prevent the progression of chronic complications.

20- Development of an extraction liquid chromatography-tandem mass spectrometry technique to quantitate the level of Dihydroceramide species in the plasma of MPS III patients

Yeniay Erdem[1], Karine Bernier[1], Jaeyeon Park[1], Farah ElTurk[1,2*] & John Mitchell[1,3,4*]

[1] Research Institute of McGill University Health Centre
[2] Centre Hospitalier Universitaire de Sainte Justine
[3] Montreal Children's Hospital
[4] McGill University

Undergraduate Student-Junior

MPS type III, also known as Sanfilippo syndrome is a lysosomal storage disorder (LSD). MPS III is caused by a deficit in one of the four enzymes required for the metabolism of a family of glycosaminoglycans, the heparan sulfate (HS). The storage of HS in cells and biological fluids inflicts detriments to one's health. Neurodegeneration and other neurological symptoms (e.g. epilepsy) have been the main symptoms observed in youth diagnosed with this syndrome. In our laboratory, we try to look for new biomarkers that can be used for early diagnosis and monitoring of disease severity and treatments. Several studies have suggested a specific group of molecules called sphingolipids as potential biomarkers for inflammation, neurodegenerative diseases and neuropsychiatric disorders. Sphingolipids belong to a class of biomolecules called lipids. They play important metabolic and structural roles in maintaining cellular homeostasis by degrading and recycling ceramide in the de novo sphingolipid synthesis pathway. Dihydroceramide, a precursor for the synthesis of ceramide, was suggested as a potential biomarker for various diseases due to its implication in cancer and metabolic conditions. Sensitive, accurate and precise methods of identification and quantification of sphingolipids are therefore crucial elements for evaluating their possible implications in disorders that could make them potential biomarkers. Hence, state-of-the-art techniques based on liquid chromatography (LC) combined with tandem mass spectrometry (MS/MS), and instruments (Xevo TqS, Waters), were applied to measure concentrations of sphingolipids in patient blood samples. Dihydroceramide as well as other families of sphingolipids were evaluated as possible biomarkers for MPS III disease.

21- The sperm epigenome in mice with the human equivalent of the MTHFR 677C>T variant and the effects of folic acid deficiency and supplementation

Edgar Martinez Duncker Rebolledo, Donovan Chan, Karen E. Christensen, Alaina M. Reagan, Gareth H. Howell, Rima Rozen, Jacquetta Trasler

MSc Student-Junior

MTHFR is an enzyme that plays a key role in providing methyl groups for DNA methylation, including during spermatogenesis. A common genetic variant in humans (MTHFR 677C>T), results in a thermolabile enzyme and has been linked to various disorders, including infertility. A new mouse model has been created introducing the human equivalent of the polymorphism using CRISPR/Cas9. Biochemical parameters in Mthfr 677TT mice recapitulate values found in MTHFR 677TT men. Our aims were: (1) to characterize the sperm DNA methylome of the Mthfr 677CC and TT mice on a control diet (CD, 2mg/kg of diet) to determine whether alterations in sperm DNA methylation are similar to those reported in the sperm of MTHFR 677TT men, and (2) to assess the effect of folic acid deficiency (FD, 0.3mg/kg of diet) on the sperm DNA methylome in both 677CC and TT animals. Adult male mice were fed CD and FD diets for four months. Body and reproductive organ weights and testicular sperm counts were determined. DNA methylation in sperm was assessed using bisulfite pyrosequencing for imprinted genes and Illumina Infinium Mouse Arrays for genome-wide profiles. Body and reproductive organs weights and sperm counts and imprinted gene methylation were unaffected by genotype or diets. Analysis of variance of array data revealed ~15,000 probes showing differences between groups. Post hoc testing demonstrated the largest effect when comparing Mthfr 677CC vs. TT genotypes with little additional impact of diet. Ongoing work is assessing effects of folic acid supplementation using whole-genome bisulfite sequencing. (Supported by CIHR)"

22- Inter-Generational Transmission Of Developmental Risk From Father To Child Through The Placental Epigenome

Julia Barnwell[1,2], Sophia Rahimi[1,2], Sherri Lee Jones[1,3], Josée Martel[1], Donovan Chan[1], Tuong-Vi Nguyen[1,3,4,5], Tina Montreuil[1,3,6,7,8], and Jacquetta Trasler[1,2,6,9]

[1] Research Institute of the McGill University Health Centre, Montreal, QC, Canada
[2] Department of Human Genetics, McGill University, Montreal, QC, Canada
[3] Department of Psychiatry, McGill University, Montreal, QC, Canada
[4] Lady Davis Institute for Medical Research, Jewish General Hospital, Montreal, QC, Canada
[5] Reproductive Psychiatry Program, McGill University Health Centre, Departments of Psychiatry and Obstetrics and Gynecology, Montreal, QC, Canada
[6] Department of Pediatrics, McGill University, Montreal, QC, Canada
[7] Department of Educational and Counselling Psychology, McGill University, Montreal, QC, Canada
[8] CHU Ste-Justine Research Centre, Montreal, QC, Canada
[9] Department of Pharmacology and Therapeutics, McGill University, Montreal, QC, Canada

MSc Student-Junior

There is increasing evidence that paternal factors such as older age and psychological stress may influence brain development in children. Pre-conception paternal factors such as age are associated with inheritable epigenetic modifications like DNA methylation in sperm that can be transmitted to the feto-placental unit. Many genes regulating placental function are paternally regulated and closely involved in children's brain and endocrine development. Paternal-age-induced epigenetic reprogramming effects during fetal development could have long-term neuroendocrine and behavioral impacts. Adrenarche is a neuroendocrine process that occurs around 6-8 years of age that represents adrenal maturation characterized by the secretion of dehydroepiandrosterone (DHEA) in the first stage of puberty. DHEA and its associated hormones are involved in cortico-limbic development, making adrenarche a key time to assess the influence of perinatal factors on child endocrine, brain and behavioral development. Our project aims to investigate whether paternal-age-induced differences in the placental epigenome may be associated with structural differences in critical brain regions regulating behavior and emotions (e.g. amygdala and hippocampus), and with differences in cognitive or behavioral outcomes in children during adrenarche. Data from the 3D (Design, Develop, Discover) prospective birth cohort, including paternal and maternal data on age, depression and anxiety, and placenta DNA methylation (Illumina 850K array, n=64) will be used, along with follow-up structural MRI and neurocognitive outcome measures from children. Analyses using moderation models will test for interactions between paternal age and placental epigenome, and structural brain measures and placental epigenome, to predict child cognition and behavioral outcomes at 6-8 years old.

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23- Parent and adolescent decisions regarding research genetic sequencing in pediatric cancer

Michelle Carter [1, 2], Lara Reichman [1, 2], Crystal Budd [2], Catherine Goudie [1, 2]

[1] Department of Human Genetics, McGill University, Montreal, Canada
[2] Child Health and Human Development Program, Research Institute of the McGill University Health Centre, Montreal, Canada

MSc Student-Junior

Introduction: In recent years, large-scale genetic sequencing (LSGS) use within pediatric oncology has been growing. LSGS includes sequencing technologies ranging from multi-gene cancer panels to whole genome sequencing (WGS). As use of this technology evolves and its clinical utility is being studied, it is important to assess all stakeholder perspectives, including those of adolescents and parents.

Methods: A scoping review was performed to describe the current landscape of research on adolescent and parent attitudes (motivations and concerns) towards participating in LSGS. A single-centre questionnaire study was then performed to assess adolescent and parent attitudes towards participating in LSGS cancer research programs at the McGill University Health Centre (MUHC).

Results: Fifteen publications were identified via the scoping review. An analysis of these publications provided evidence of gaps in the study on perspectives from (a) families in Canadian contexts and (b) adolescent patients. The most frequently reported motivations among the publications were altruism and improved treatment. The most frequently reported concern was insurance discrimination.
Seven individuals participated in the MUHC study, including 6 parents and 1 adolescent. All respondents had elected to participate in LSGS. Information seeking and altruism were identified as important motivations in their LSGS decision-making, consistent with the scoping review. No concerns, including insurance discrimination, were reported as important.

Conclusions: Individuals considering LSGS after a pediatric cancer diagnosis may weigh multiple motivations and/or concerns, depending on the context. More research is needed to better understand adolescent and parent attitudes, both at the MUHC and more broadly.

24- Association between Endometriosis and Risk of Preeclampsia in Women Who Conceived Spontaneously: A Systematic Review

Katherine Drummond [1,2], Neda Mohammadi Danesh[1,2], Sophie Arseneault[1,3], Julia Rodrigues[4], Togas Tulandi[1,2], Jason Raina[1,2], Eva Suarthana[1,2]

[1] Faculty of Medicine and Health Sciences, McGill University, Montreal, Quebec, Canada
[2] Department of Obstetrics and Gynecology, McGill University, Montreal, Quebec, Canada
[3] Faculty of Arts, McGill University, Montreal, Quebec, Canada
[4] Department of Family Medicine, McGill University, Montreal, Quebec, Canada

Medical Student-Junior

Association between endometriosis and the subsequent development of preeclampsia are inconclusive, and most studies do not account for the confounding influence of assisted reproductive technologies (ART). We performed a systematic review evaluating the association between endometriosis and the risk of preeclampsia in women who conceived spontaneously. We also investigated the association between endometriosis and the risk of other maternal outcomes.

We systemically searched for observational studies published on PubMed, MEDLINE, EMBASE, Scopus, Cochrane Library, Web of Science, and Google Scholar from inception until November 2021. Inclusion criteria included spontaneous conception and surgical and/or imaging ascertainment of an endometriosis diagnosis. Exclusion criteria included conception using ART, multiple pregnancies, chronic hypertension, and unclear diagnoses of endometriosis. Data of selected studies were extracted, and analysis was performed on Review Manager (RevMan), version 5.4. Quality assessment of included studies for potential risk of bias was evaluated using the Newcastle–Ottawa Scale (NOS) for cohort studies.

Of 610 identified articles, three cohort studies of spontaneous pregnancies were included. Endometriosis was associated with an increased risk of preeclampsia (RR = 1.45, 95% CI 1.13–1.88, P = 0.004, I2 = 0%, n=3 studies). A sensitivity analysis excluding a study with adenomyosis cases yielded similar risk (RR = 1.44, 95%CI 1.11–1.87, P = 0.006, I2 = 0%, n=2 studies). Having endometriosis did not significantly increase risk of caesarean delivery (RR = 1.38, 95%CI 0.99–1.92, P = 0.06, I2 = 80%, n=2 studies), or post-partum hemorrhage (RR = 1.16, 95%CI 0.46–2.91, P = 0.76, I2 = 50%, n=2 studies).

To conclude, women with endometriosis who conceive spontaneously are at increased risk of preeclampsia but may not be at increased risk of other adverse maternal outcomes.

25- Postnatal Development of Spermatogonial Stem Cells

Youngmin Song, Xiangfan Zhang, Makoto Nagano

MSc Student-Junior

Spermatogonial stem cells (SSCs) are the foundation of spermatogenesis and drive sperm production throughout adult life. They are a crucial resource for fertility preservation, particularly for prepubertal boys who undergo gonadotoxic treatment. While these patients do not produce sperm to cryopreserve, in theory, SSCs can be isolated from their testes before treatment and transplanted later to restore fertility. Using the mouse model, we determined the cell-surface immunophenotypes of SSCs during postnatal development, as a step towards purifying prepubertal SSCs. We prospectively isolated SSC-enriched germ cells at three stages of development (0-2, 8-9, and 16-18 dpp) using Fluorescent-Activated Cell Sorting (FACS). We identified various cell fractions at each stage by the expression of two SSC markers (Integrin-α6, Thy1) and two fate markers (GFRα1, c-kit). Cells in each fraction were assayed for their SSC activity and for the expression of intracellular molecules at protein and transcript levels. We discovered that prepubertal germ cells exhibited unique immunophenotypic profiles that are specific to each stage of development, allowing us to identify the cell fractions with different levels of SSC activity. For instance, the SSC frequency was 300-fold greater in the Thy1-positive fraction at 8-9 dpp versus unsorted adult testis cells. The Thy1-negative fraction, which emerged at 8-9 dpp, showed much lower SSC activity, reflecting a transition step of SSC fate commitment towards exiting stem cell state. Our goal is to further dissect this process to better understand the fate commitment steps and mechanisms during postnatal development of SSCs.

26- Radiological and etiology profile of children with pontocerebellar hypoplasia

Maisa Malta, Royaha Binti Mohamad Zakaria , Nassima Addour, Christine Saint Martin, Myriam Srour

Volunteer Researcher-Junior

Background: The term Pontocerebellar hypoplasia (PCH) was initially used to designate a heterogeneous group of fetal onset genetic neurodegenerative disorders. As a descriptive term, PCH refers to pons and cerebellum of reduced volume. Currently, there are 17 types of PCH described associated with over 20 different genes. In addition to the classic PCH types, many other disorders can result in a similar imaging appearance, including acquired etiologies.

Methods: We performed a retrospective chart review of patients with radiologic evidence of PCH. This study was approved by our Institutional Research Ethics Board.

Results: 28 cases were included, 16 males and 12 females, with ages ranging between 8 days to 15 years. The median follow-up period was 3 years 6 months (ranging from 2 months to 15 years). All individuals in our cohort had hypoplasia of the pons. The cerebellar vermis was hypoplastic in 27 individuals, and atrophic in 1 individual. Overall, 64% of patients had cerebellar hemisphere hypoplasia and 14% had other types of cerebellar anomalies. On coronal view, 64% had the butterfly pattern and only 8% had a dragonfly pattern appearance. Supratentorial anomalies were common and included delayed myelination or non-specific white matter signal anomaly (57%), cortical migration anomaly or simplification of gyral pattern (26%) and ventriculomegaly (32%).

An underlying etiology was identified in 71% of cases. 21% had chromosomal abnormalities, 32% had monogenic disorders and 18% had acquired etiologies. Interestingly, none of our patients had pathogenic variants in classic PCH genes.

Conclusion:
PCH is a condition with very heterogenous imaging and clinical symptoms. Its etiology includes both genetic and acquired causes. Therefore, broad genetic testing, including chromosomal microarray and exome-based panels, is highly recommended in individuals with PCH-like imaging appearance.

27- Identifying Pathogenic Variants in the Primary Ovarian Insufficiency Genes of Patients Experiencing Recurrent Pregnancy Loss or Infertility

Zeynep Yalcin[1,2], Rima Slim[1, 2, 3]

[1] Division of Human Genetics, McGill University, Montreal, Canada.
[2] Child Health and Human Development Program, Research Institute of the McGill University Health Centre, Montreal, Canada.
[3] Department of Obstetrics and Gynecology, McGill University, Montreal, Canada.

MSc Student-Junior

Primary ovarian insufficiency (POI) is the cessation of normal ovarian function before age 40. POI affects roughly 1% of women under 40, and 0.1% of women under 30. It is characterized by amenorrhea and gonadotropic hormone deficiency, which lead to suboptimal oocyte quality, miscarriages, and infertility. Although a highly heterogenous condition, previous data have implicated a strong genetic component in POI. Thus, genetic screening is crucial in families failing to conceive.

In this study, we identified POI gene variants in families experiencing recurrent pregnancy loss and infertility, who have not received a previous POI diagnosis. Next generation sequencing was used to sequence patient exomes and retrieve variant information. Mutations in genes involved in various aspects of female reproduction were targeted and sequenced via Sanger sequencing. We prioritized protein truncating mutations, such as frameshift, stop-gain, and insertion/deletion. Validated variants were later segregated in patient's family members. In the upcoming stages of the study, the allele frequency of the variants confirmed in our patients will be compared with the variants' allele frequency in the general population. A higher frequency of protein-truncating variants in patients will show that the patients analyzed are genetically susceptible to POI.

Finding pathogenic variants in the POI genes of these patients will provide them with the appropriate diagnosis, further improving the management of their case and reducing the expenses spent on unsuitable fertility treatments. Results from this study can additionally contribute to developing diagnostic genetic tests and provide better support for the patients."

28- Diabetes Duration and Glycemic Control in Adolescents with Type 1 Diabetes: A Cross-Sectional Study

Olivier Renaud-Charest[a,b], Elise Mok[b], Jennifer Frei[b], Marie-Laurence Brunet[a,b], Melanie Henderson[c,d,e], Elham Rahme[b,f], Kaberi Dasgupta[b,f], Meranda Nakhla[b,g]

[a] Faculty of Medicine and Health Sciences, McGill University, Montreal, Québec, Canada, H3G 2M1
[b] Centre for Outcomes Research and Evaluation, Research Institute of the McGill University Health Centre, Montreal, Québec, Canada, H4A 3J1
[c] Department of Pediatrics, Université de Montréal, Montreal, Québec, Canada, H3T 1C5
[d] CHU Sainte-Justine Research Centre, Montreal, Québec, Canada, H3T 1C5
[e] School of Public Health, Department of Social and Preventive Medicine, Université de Montréal, Montreal, Québec, Canada, H3N 1X9
[f] Division of Clinical Epidemiology, Department of Medicine, McGill University, Montreal, Québec, Canada, H4A 3J1
[g] Division of Endocrinology, Department of Pediatrics, McGill University Health Centre, Montreal, Québec, Canada, H4A 3J1

Medical Student-Junior

Objectives: Evidence is lacking on whether diabetes duration influences comfort with diabetes management in adolescents with type 1 diabetes (T1D) prior to the transfer from pediatric to adult care. We examined associations of diabetes duration with diabetes management dimensions (self-efficacy, transition readiness, diabetes distress) as well as glycemic control in late adolescence.

Methods: Using a cross-sectional design, we conducted a secondary analysis of baseline data of adolescents (ages 16-17 years) with T1D followed at pediatric diabetes academic hospitals in Montreal and enrolled in the Group Education Trial to Improve Transition (GET-IT-T1D). Participants completed validated questionnaires on self-efficacy (Self-Efficacy for Diabetes Self-Management Measure [SEDM], score 1 to 10), diabetes distress and transition readiness, as well as an A1c capillary blood test. The primary outcome was self-efficacy. We examined associations of diabetes duration with diabetes management dimensions and A1c using regression models adjusted for sex, socioeconomic status, insulin pump use, glucose sensor use, and psychiatric comorbidity (eating disorders, depression, anxiety, attention deficit disorder, other).

Results: Of 203 adolescents with T1D, mean diabetes duration (SD) was 7.57 (4.44) years. SEDM score was 6.83 (1.62). Diabetes duration was not associated with self-efficacy, diabetes distress or transition readiness. Adolescents with a longer diabetes duration had higher A1c (adjusted β, 0.107; 95% CI, 0.053 to 0.161).

Conclusions: Whereas diabetes duration is not associated with diabetes management dimensions, adolescents with longer diabetes duration are at risk for higher A1c and may need additional support to improve glycemic control before transition to adult care.

29- Exploring the Gap: A Survey of the Digital Divide at the Montreal Children's Hospital

Maira Corinne Claudio[a], Zachary Rehany[a], Katerina Stachtari[b], Elena Guadagno[b], Esli Osmanlliu[c], Dan Poenaru[a,b]

[a] McGill University, Faculty of Medicine and Health Sciences, Montreal, Canada
[b] Harvey E. Beardmore Division of Pediatric Surgery, The Montreal Children's Hospital, McGill University Health Center, Montreal, Canada
[c] Division of Pediatric Emergency Medicine, Department of Pediatrics, The Montreal Children's Hospital, McGill University Health Centre, Montreal, Canada

Medical Student-Junior

Mobile health apps have gained popularity for patient care and communication. However, inequitable access to digital technology risks widening health disparities if inclusivity is not a consideration in the design. There is limited data on the digital divide among families of children treated in a tertiary care setting. The data can inform an equitable design for upcoming digital health interventions.

We developed a survey to assess the level of internet access, smartphone use and readiness to use mobile health apps. This was specifically among caregivers visiting the pediatric surgical clinics and emergency department at our tertiary pediatric institution. The questionnaire was designed using experience-based co-design, through a series of structured team interactions with patient partners, followed by cognitive testing and piloting. Questions were adapted from validated tools.

Out of the 204 respondents, 5 (2%) reported not having internet or smartphone access and 2%(5) of people with internet access rated their connectivity as 'bad' or 'very bad'. The reason for not having access was primarily financial, followed by a lack of interest. Of the 5 people who did not own a smartphone, 3 had a member in their household who did own one, and all 5 were above the age of 45. Twenty-five participants (13%) were uncomfortable using their smartphones, 9 (4%) were unaware of how to download an app, and 15 (7%) did not know how to use common smartphone apps or features. Regarding app readiness, over 95% of participants affirmed that they would use a health app if available and it would be useful for themselves or their families. Meanwhile, 11 (6%) were unwilling to communicate with their doctor online. Of the 49 short text responses regarding potential health app concerns, 31 included app security and confidentiality. Frequent suggestions by participants included the ability to communicate efficiently with their healthcare providers, appointment scheduling, task/appointment reminders, updated wait-room wait times, and, most commonly, high user-friendliness and app simplicity.

Although most families reported sufficient internet access and digital comfort to use mobile health apps, some struggled with prohibitive costs and device access. Respondents emphasized ease of use for mobile apps and online privacy concerns. The study has identified opportunities for advocacy and educational interventions to promote digital health access and informs the development of future health apps

30- The Role of Odd-skipped Related 1 in Bladder Dysfunction from Spinal Cord Injury

Carlos Agustin Isidro Alonso, Vasikar Murugapoopathy, Laura Curran, Samuel David, Indra Gupta

Post-Doctoral Fellow-Senior

Innervation of the bladder is disrupted in patients with spinal cord injury (SCI). This results in a bladder with high pressure that can't empty. In response, fibroblasts in the lamina propria and muscle layer upregulate collagen deposition, leading to a fibrotic bladder with reduced capacity. The molecular bases of bladder fibrosis in response to SCI are poorly understood. The transcription factor Odd skipped related-1 (Osr1) is expressed in mesenchymal progenitor cells that become activated and self-renew during development and injury-repair in skeletal muscle and the liver. We hypothesize that upon SCI, Osr1 regulates mesenchymal progenitors that differentiate to fibrogenic progeny responsible for collagen secretion in the bladder. To test this, we performed a moderate SCI or sham surgeries in mice and examined bladder function and histology at 2 and 4 weeks after surgery. At both timepoints, the bladders from SCI animals displayed hypertrophy of the lamina propria and muscle layer, and increased collagen deposition compared to bladders from intact animals. Additionally, animals from the SCI group at 2 weeks showed an increased number of voiding events per unit of time, which may be reflective of a hyperactive bladder. In the future we will perform lineage tracing experiments to determine the fate of Osr1+ progenitors and their progeny in bladder disease from SCI. Results from this work will provide mechanistic insight into how bladder fibrosis arises and may result in new therapeutic targets to preserve bladder function in patients with SCI.

31- The Effect of Previous Surgery on Magnetic Source Reconstruction in Pediatric Drug-Resistant Epilepsy

Eleanor Hill[1], Jeremy Moreau[1,2,3], Erica Minato[1], Marc Lalancette[1], Elisabeth Simard-Tremblay[4], Roy Dudley[2], and Sylvain Baillet[1]

[1] Montreal Neurological Institute and Hospital, McGill University, Montreal, QC, Canada
[2] Department of Pediatric Surgery, Division of Neurosurgery, Montreal Children's Hospital, Montreal, QC, Canada
[3] Cumming School of Medicine, University of Calgary, Calgary, AB, Canada
[4] Department of Pediatrics, Division of Pediatric Neurology, Montreal Children's Hospital, McGill University, Montreal, QC, Canada

PhD Student-Senior

Background: Focal epilepsy surgery requires accurate localization of the epileptogenic zone. This remains extremely challenging in poorly-defined cases (i.e., lesion-negative imaging) such that ~50% suffer from recurring seizures, sometimes requiring a repeat presurgical evaluation, for which magnetoencephalography (MEG) is a well-accepted component. A previous study raised concerns that cerebrospinal fluid (CSF)-filled cavities (i.e., resections) could alter magnetic source localization, calling into question the utility of MEG for such cases. We hypothesized that such effects would be observed in pediatric epilepsy patients who have undergone a previously failed surgery, but that different source reconstruction methods could overcome these challenges.

Method: We used MEG rest recordings of pediatric epilepsy patients undergoing presurgical evaluation and who had undergone a previously failed epilepsy surgery (n=6). Magnetic source imaging of epileptiform activity was performed for different combinations of source reconstruction methods (overlapping spheres (OS) and finite element model (FEM)) and anatomies (individual and generic).

Results: We observed a shift of source maps between OS and FEM methods for both anatomies, with more pronounced effects when using generic anatomical models. We found that the source maps obtained with FEM on generic anatomy are better aligned with those derived from FEM on individual anatomy than their OS versions.

Discussion: Our qualitative observations so far indicate that surgical cavities affect how epileptiform activity is mapped from subsequent MEG recordings. We foresee that they should be factored into source reconstruction. More cases and further quantification of source displacements against controls (i.e., those without surgical cavities) are needed before suggesting a new source reconstruction protocol for epileptiform activity. "

32- Odd skipped related 1 (Osr1) regulates mesenchymal patterning during bladder development

Vasikar Murugapoopathy and Indra R. Gupta

PhD Student-Senior

The bladder is a muscular sac that can expand 4-fold when full and withstand high pressure during emptying. These properties are due to the collagen-rich lamina propria layer and the smooth muscle layer which consists of circular and longitudinal bundles. Although both the lamina propria and muscle are derived from bladder mesenchyme, the signaling pathways and transcription factors that regulate its differentiation are not well understood. Sonic hedgehog (Shh) is secreted from the endodermal epithelia of the primitive bladder and establishes a gradient which patterns the adjacent mesenchyme: the inner mesenchyme becomes the lamina propria, while the outer mesenchyme becomes the smooth muscle. Odd-skipped related 1 (Osr1) is a transcription factor that defines mesenchymal cell populations in several tissues where it functions downstream of the Shh pathway. Because Osr1 is strongly expressed in bladder mesenchyme, we hypothesized that it is required for mesenchymal differentiation. At embryonic day (E)14, when bladder mesenchyme begins to differentiate, Osr1-/- embryos did not express alpha smooth muscle actin (□SMA) by immunofluorescence, unlike Osr1+/- and Osr1+/+ embryos. At E15.5, a small bladder with a thin muscle layer and decreased expression of □SMA was detected in Osr1-/- embryos. Furthermore, the muscle was not organized into circular and longitudinal muscle bundles as in Osr1+/- and Osr1+/+ embryos. Osr1-/- embryos also lacked Collagen I in the lamina propria, which is produced by fibroblasts. No differences in the amount of cell proliferation or cell death were noted at these stages. This suggests that loss of Osr1 results in a defect of mesenchymal cell differentiation. To determine the impact of Osr1 removal on later stages of bladder development we will remove Osr1 specifically from the mesenchyme.

33- Connecting Claudin-3 dependent molecular mechanisms to morphogenetic events of neural tube closure

Elizabeth-Ann Legere[1,2] and Aimee Ryan[1,2]

[1] Department of Human Genetics, McGill University
[2] Research Institute of McGill University Health Centre

PhD Student-Senior

Proper neural tube development is essential for the formation of the brain and spinal cord. The neural tube begins as a flat sheet of epithelial cells whose edges, the neural folds, elevate upwards and fuse along the dorsal midline of the embryo. In chick embryos, depletion of the apical tight junction protein, Claudin-3 (Cldn3), causes spinal neural tube defects due to failure in neural fold fusion. The cytoplasmic domain of Cldn3 interacts with tight junction cytoplasmic proteins, bridging the cell-cell junction to signalling pathways and the cytoskeleton. I hypothesize that Cldn3 regulates apical localization of proteins essential for morphogenetic cell behaviors of spinal neural fold fusion. To better understand morphogenetic events in neural fold fusion, specifically changes in cell shapes, movements, and cell-cell junctions, I am characterizing wild-type and Cldn3-depleted chick neural fold fusion using live imaging, scanning electron microscopy (SEM), and immunofluorescence. Preliminary results suggest that the process of neural fold fusion differs between the cranial and spinal regions. Live imaging revealed that the neural folds in the future spinal region of the embryo fuse in a different process than cranial neural folds, suggesting a role of Cldn3 is spinal-specific neural fold fusion. By SEM there were fewer thread-like protrusions in the spinal region of the embryo compared to the cranial. These thread-like protrusions were absent in Cldn3-depleted embryos along with increased of membrane blebbing. Due to changes in apical membrane morphology, I examined apical protein localization patterns using immunofluorescence. I found that Cldn3-depleted embryos display altered increased apical aggregates of Rac1, a protein involved in membrane protrusions, Par-3, an apical polarity protein, and all apically expressed membrane N-glycoproteins. This research is working towards a better understanding of the morphogenetic events of neural fold fusion identifying the mechanisms of the molecular role of Cldn3.

34- Heterozygous deletion of Snrpb in murine neural crest cells causes splicing aberrations that result in craniofacial abnormalities, which mimics those seen in Cerebrocostomandibular syndrome (CCMS)

Sabrina Alam, Shruti Kumar, Marie-Claude Beauchamp, Eric Bareke, Alexia Boucher, Nadine Nzirorera, Yanchen Dong, Reinnier Padilla, Si Jing Zhang, Jacek Majewski, Loydie A. Jerome-Majewska

PhD Student-Senior

Patients with congenital rare disease, Cerebrocostomandibular syndrome (CCMS) carry heterozygous mutations in a core splicing component named SNRPB and mainly show craniofacial and rib defects. It is unknown why mutations in this core component of splicing machinery result in specific craniofacial abnormalities in CCMS patients. To understand the molecular etiology of the craniofacial malformations seen in CCMS, we generated a mouse line with a conditional mutation in Snrpb and showed that heterozygous mutation of Snrpb is deleterious in mouse before morphogenesis. We recapitulated the craniofacial anomalies in mice by introducing Snrpb heterozygous mutation in the neural crest cells (Snrpbncc+/-). Snrpbncc+/- mutants showed abnormal craniofacial development with variable penetrance and expressivity and died between Embryonic day (E)17.5 and birth. We found increased cell death in the head region of the Snrpbncc+/- mutants along with increased active P53 in the nucleus. RNA sequencing analysis of the mutants' heads revealed that the P53 pathway was upregulated in the mutants and showed increased exon-skipping events in two negative regulators of P53- Mdm2 and Mdm4, among many other aberrantly spliced genes. Though these findings suggest that the etiology of craniofacial abnormalities in the mutants is through P53 mediated apoptosis, partial or complete removal of P53 from neural crest cells do not restore normal craniofacial development in Snrpbncc+/- mutants. We also found increased exon skipping in several genes important for craniofacial development and showed aberrant expression pattern of genes key important for facial morphogenesis such as Shh, Msx2 and Fgf8. We suggest that craniofacial malformations found in CCMS patients are likely a combined consequences of P53-mediated apoptosis and misexpression of important genes for craniofacial morphogenesis, due to anomalous splicing.

35- Nursing Challenges in the Neonatal Intensive Care Unit Through Healthcare Providers' Lenses

Alice Tao Ran Guo[1], Elias Jabbour[1], Elissa Remmer[1], Martine Claveau[1], Anie Lapointe[2], Marc Beltempo[1]

[1] Montreal Children's Hospital, McGill University
[2] CHU Sainte-Justine, Université de Montréal

Medical Student-Junior

INTRODUCTION. Extremely preterm infants born at <29 weeks' gestation are admitted in tertiary neonatal intensive care units (NICUs) to receive specialized care. Previous research showed associations between better nurse-to-patient ratios and better outcomes, yet many NICUs face understaffing. This study aimed to explore healthcare providers' perceptions of nursing ratios for extremely preterm infants and potential mitigation measures in periods of understaffing.

METHODS. This web-based bilingual 17-question survey was distributed by email through chain-referral to nurses, nurse practitioners, neonatologists and respiratory therapists currently practising in one of Quebec's six tertiary NICUs between August and October 2022. The survey explored perceptions of ideal nurse-to-patient ratios, nurse staffing, associations of nursing ratios with outcomes, and understaffing's impact on work performance and work environments. Analysis was conducted using descriptive statistics.

RESULTS. 250 providers from all six tertiary NICUs in Quebec completed the survey. The proportion of providers recommending one-to-one nursing in the first three days of admission for extremely preterm infants varies based on gestational age (74% for <25w, 61% for 25-26w, 34% for 27-28w in intubated infants) and clinical status (39% for CPAP, 61% for intubation, 84% for intubation+vasopressor in infants 25-26w). Nursing ratios are perceived to directly impact outcomes, especially for better grief support, better psychosocial support, decreased medication errors and better parent teaching (75%, 66%, 64%, 62% for strong agreement). However, 74% of providers perceive >40% of nursing shifts in their unit as understaffed. With high unit activity, self-care and communication with families were most affected; self-care and discharge planning were most deprioritized. When understaffed, providers reported requiring more help for discharge planning, communication with families and documentation, suggesting that support with these tasks could mitigate periods of high unit activity.

CONCLUSION. Clarifying providers' perception of high unit activity and its impact on patient care could guide mitigation strategies and improve work environments."

36- Nodal expression in the uterus during the preimplantation period is required for leukocyte infiltration and endometrial receptivity

Sarah Yull[1,2], Shiva Shafiei[1,2], Daniel Dufort[2,3]

[1] Division of Experimental Medicine, McGill University
[2] Child Health and Human Development Program. McGill University Health Centre
[3] Department of Obstetrics and Gynecology, McGill University, Montreal, Canada

PhD Student-Senior

In recent years, the average age women attempt to conceive their first child has trended upwards. Unfortunately, an unintended consequence of advanced maternal age is a higher risk of fertility complications. It is estimated that one in six couples experience infertility, which has resulted in a greater reliance on assisted reproductive technologies. Infertility, as well as pathological complications have been extensively correlated with inadequate uterine immune environments. Recently, we have provided evidence that Nodal is expressed in the pregnant mouse uterus, and has functions in pregnancy outcome, placental development and the timing of parturition. Here, we utilize a reproductive-tract specific conditional knockout mouse model (Nodal□/□) to understand how Nodal supports implantation. It was determined that Nodal□/□ females have a 50% implantation failure rate, with fetal loss occurring later in pregnancy. Although females have normal reproductive morphology, estrus cycling and viable embryos prior to implantation, the expression of endometrial receptivity genes, cytokines and growth factors are dysregulated. Additionally, increased infiltration of monocytes and macrophages coupled with a decrease in the population of T cells could create a pro-inflammatory environment unfavourable for implantation. It has been previously reported that disruption to components of the Nodal signalling pathway has been implicated in cases of implantation failure and unexplained infertility in humans. We hypothesize that Nodal is required as immunomodulator of pregnancy, and its dysregulation contributes to infertility.

37- Deletion of SF3B4 In Neural Crest Cells Encapsulates the Variable Expressivity of Craniofacial Abnormalities Observed in Nager and Rodriguez Syndrome Patients

Shruti Kumar[1], Sabrina S. Alam[1], Marie-ClaudeBeauchamp[3], Jacek Majewski[1] and Loydie Jerome-Majewska[1,2,3]

[1] Department of Human Genetics, Faculty of Medicine, McGill University, Montreal, QC Canada
[2] Department of Anatomy and Cell Biology, Faculty of Medicine, McGill University, Montreal, QC Canada
[3] Research Institute of the McGill University Health Centre, Montreal, QC Canada

PhD Student-Senior

Recently, both Nager syndrome and Rodriguez syndrome patients were identified to carry rare mutations in SF3B4. Both disorders affect the face as well as the limb including both hands and feet. Nager syndrome patients survive and exhibit smaller jaw bones, smaller cheek bones, cleft palate, hearing problems as well as downward slanted eyelids. However, Rodriguez syndrome is much more severe, and patients often die before or soon after birth. We hypothesized that craniofacial abnormalities associated with reduced SF3B4 levels is due to tissue-specific expression and requirement of this gene in neural crest cells. To generate a conditional mutant mouse line for Sf3b4, we used CRISPR/Cas9 to insert LoxP sequences in intron 1 and 3 of this gene. To test our hypothesis, we mated Sf3b4 conditional mutant mice to Wnt1-Cre2 transgenic mice to delete exons 2 and 3 specifically in neural crest cells. Heterozygous mutant embryos from these matings were normal. Sf3b4L/L;Wnt1-Cre2 embryos have brain and craniofacial abnormalities, including abnormal forebrain, midbrain and hindbrain, hypoplasia of the maxillomandibular region, midline cleft as well as middle ear abnormalities. Majority of these embryos die before birth and the few mutants that are born are indistinguishable from their wildtype littermates. Thus, neural crest specific deletion of Sf3b4 in mice is able to model the craniofacial abnormalities presented in patients as well as capture the variable expressivity observed. Our model can further be used to uncover the splicing and molecular events regulated by SF3B4 during craniofacial development.

38- Protective role of interleukin-1 blockade on Group B Streptococcus-induced chorioamnionitis and autistic traits in male progeny

Taghreed A. Ayash[1], Marie-Julie Allard[1], Guillaume Sébire[1]

[1] Department of Pediatrics, McGill University, Montreal, Quebec, Canada
[2] Department of Pharmacology, McGill University, Montreal, Quebec, Canada

Post-Doctoral Fellow-Senior

Group B Streptococcus (GBS) is one of the most common bacteria responsible of maternofetal and neonatal infections during pregnancy. Dam inoculated with GBS at the end of gestation develop chorioamnionitis. Such placental inflammation is mainly featured by the activation of the interleukin-1 (IL-1) pathway. Offspring in utero-exposed to GBS chorioamnionitis, develop brain injuries leading to neurobehavioral impairments such as autism. Both human and rodents male offspring are at greater risk than females to develop autistic traits. Hence, we hypothesised that IL-1 blockade at the time of GBS-induced chorioamnionitis alleviates placental inflammation, and neurobehavioural impairments in rat offspring. Our results showed that IL-1Ra reduced: (1) the IL-1□ titer in the pups sera of GBS-infected dams, (2) autistic traits in GBS-exposed male progeny, and (3) brain cell apoptosis in male rats in utero-exposed to GBS-induced inflammation. Our finding showed the key role of IL-1 as placento-, foeto-, and neuro-protective agents in the context of GBS-induced chorioamnionitis.
This research was supported by a CIHR grant.

39- Influence of androgens on the innate immune system

Seline Vancolen, Guillaume Sébire, Bernard Robaire

PhD Student-Senior

The nature and strength of the mammalian immune response varies between males and females. Males are more susceptible to higher rates of infection by bacteria, viral and parasitic pathogens, whereas a higher incidence of autoimmune diseases exists in females (1-3). There are many explanations as to why this sex difference in immune function exists. Aside from the biological differences between males and females due to sex chromosomal complement, it is known that sex hormones can also directly influence immune cell functions (4, 5). While it is generally accepted that androgens in males elicit suppressive effects on the immune system, conflicting data exist for androgens, where both pro- and anti-inflammatory effects have been demonstrated (6,7). In addition to the presence of conflicting evidence in the literature, much research has been focused on adaptive immunity, with fewer studies focused on the initial stages of the inflammatory response. It is therefore important that this data gap in the interplay between the endocrine and immune system be investigated. The objective of this review is to identify the current state of knowledge regarding the role of androgens in shaping such sex-dependent differences in the innate immune response.

40- Modeling Cerebro-costo-mandibular Syndrome (CCMS) with Tamoxifen-Induced Snrpb Deletion

Yanchen Dong[1,2], Sabrina Shameen Alam[1,2], Loydie A. Jerome-Majewska[1,2,3,4]

[1] Research Institute of the McGill University Health Centre at Glen Site, Montreal, QC H4A 3J1, Canada
[2] Department of Human Genetics, McGill University, Montreal, QC H3A 0G1, Canada
[3] Department of Anatomy and Cell Biology, McGill University, Montreal, QC H3A 2B2, Canada
[4] Department of Pediatrics, McGill University, Montreal, QC H4A 3J1, Canada

PhD Student-Senior

Heterozygous mutations in SNRPB, an essential core component of the five small ribonucleoprotein particles of the spliceosome, are responsible for Cerebro-costo-mandibular Syndrome (CCMS). CCMS is a rare congenital disorder commonly characterized by micrognathia (abnormally small jaw), cleft palate, and various degrees of rib abnormalities. Previously, we found that Snrpb heterozygous mouse embryos arrest shortly after implantation. Although heterozygous deletion of Snrpb in the developing brain and neural crest cells modeled craniofacial malformations found in CCMS patients, a model that can capture the full spectrum of CCMS symptoms is still lacking. Utilizing the tamoxifen (TAM) inducible Cre recombinase system, we generated heterozygous Snrpb deletion mid-gestation via tamoxifen injection. Here we characterized the phenotypes of mutant embryos with tamoxifen-induced Snrpb deletion from different developmental stages. Notably, in E17.5 mutant embryos, we identified CCMS-like rib abnormalities in addition to craniofacial malformations. Tamoxifen-induced deletion of Snrpb throughout the embryonic body, in all cell types, generates a better model of CCMS. By characterizing the etiology of observed abnormalities in this model, we look to identify disrupted transcripts and pathways with, potentially, greater clinical implications.

41- Rare variants in syndromic ciliopathy genes as novel causes of isolated renal disease in adults

Zachary Sentell[1,2], Lina Mougharbel[2], Zachary Nurcombe[1,2], Jean-Baptiste Rivière[2], Sima Babayeva[3], Natascia Anastasio[1], Murielle M. Akpa[2], Lee Lee Chu[2], Paul R. Goodyer[1,2,4], Elena Torban[1,2,3], Thomas M. Kitzler[1,2,5]

[1] Department of Human Genetics, McGill University, Montreal, Canada
[2] The Research Institute of the McGill University Health Centre, Montreal, Canada
[3] Department of Medicine, McGill University Health Centre, Montreal, Canada
[4] Department of Pediatrics, McGill University Health Centre, Montreal, Canada
[5] Division of Medical Genetics, McGill University Health Centre, Montreal, Canada

PhD Student-Senior

Background:
It is estimated that at least 10% of adult chronic kidney disease (CKD) is genetic. Renal ciliopathies are a frequent genetic cause of end-stage renal disease in the first three decades of life, often as part of a syndromic phenotype. However, their true genetic contribution to adult CKD may be underestimated, as some individuals present with a late-onset non-syndromic phenotype. This phenotypic variability may be due to hypomorphic variants in established ciliopathy genes that are not identified on clinical testing.

Methods:
Using next-generation sequencing, we identified rare variants in ciliopathy genes in two adults with isolated CKD. Functional analysis and patient-derived cell models revealed potential causal genotype-phenotype relationships.

Results:
Case 1: Compound heterozygous missense variants (p.P168L; p.T2079M) in C2CD3 were identified in a proband with isolated CKD. Pathogenic variants in C2CD3 cause oral-facial-digital syndrome XIV (OFD14; OMIM# 615948), but no cases of isolated renal disease were reported. Using patient-derived skin fibroblasts and urinary renal epithelial cells, we show reduced cilia length, impaired sonic hedgehog signalling, and reduced localization of C2CD3 to the basal body, when compared to healthy control cells. Notably, ciliogenesis appeared more severely affected in proband renal cells compared to fibroblasts, suggesting a renal-specific defect. Case 2: Pathogenic variants in CC2D2A cause at least four different syndromic ciliopathy disorders, but with no reported cases of isolated renal disease. We identified a homozygous nonsense variant (p.R34*) in CC2D2A in an adult patient with isolated CKD. Crucially, this variant does not affect all CC2D2A protein-coding transcripts. Using public data, we show that transcripts harbouring this variant are predominantly expressed in the kidney, but not in other tissues typically involved in syndromic phenotypes.

Conclusion:
Rare variants in syndromic ciliopathy genes may constitute novel causes of isolated renal disease in adults due to hypomorphic and renal specific effects.

42- Epigenetic Regulation of Gonadal Sex Determination and Reversal in the B6.Y(Tir) Mouse

Jiangqin Cao[1,2,3], Zongping Liu[1], Jiaqiao Zhu[1,2], Teruko Taketo[2,3,4]

[1] College of Veterinary Medicine, Yangzhou University, Yangzhou, Jiangsu, China
[2] Department of Biology, McGill University, Montreal, Quebec, Canada
[3] Research Institute of McGill University Health Centre, Montreal, Quebec, Canada
[4] Department of Surgery, McGill University, Montreal, Quebec, Canada

PhD Student-Senior

In the XY mouse such as the C57BL/6J(B6) strain, the Y-linked gene *Sry* is expressed in the gonadal primordium at 11.0 - 12.0 days postcoitum (dpc) and upregulates *Sox9*, which in turn upregulates multiple genes to support morphological testicular differentiation. In the consomic B6.Y(TIR) mouse, although both *Sry* and *Sox9* genes are upregulated on time, morphological testicular differentiation does not follow and instead ovaries or ovotestes develop. The rate of XY females carrying bilateral ovaries declines with maternal age, suggesting the epigenetic regulation of gonadal sex differentiation. This study aimed to delineate the mechanism underlining the determination of ultimate gonadal sex in the B6.Y(TIR) mouse. Histological sections with immuno-staining showed that *SOX9*-positive cells formed testis cords in the B6.XY gonads whereas FOXL2-positive cells were scattered in the B6.XX gonads at 12.5 dpc or later. By contrast, both SOX9- and FOXL2-positive cells were scattered over B6.Y(TIR) gonads at 12.5 dpc (n=6). At 13.5 dpc, *SOX9*-positive cells formed testis cords in the central region while FOXL2-positive cells clustered at both poles in B6.Y(TIR) ovotestes, whereas SOX9-positive cells disappeared and FOXL2-positive cells occupied the entire XY ovaries. When gonads were isolated at 12.5 dpc and cultured for 3 days, all B6.XY testes (n=10) retained testicular structures whereas all B6.Y(TIR) gonads (n=6) differentiated into ovaries. These results indicate that both testicular and ovarian differentiation pathways coexist in a developmental time window of 12.5-13.5 dpc, and suppression of the ovarian differentiation pathway appears to be the key for facilitating testicular differentiation in the B6.Y(TIR) gonad.

43- Characterization of focal cortical dysplasia using single nucleus RNA sequencing

Zahra Bahmanpour[1,2], Lina Mougharbel[2], Nassima Addour[2], Spyridon Oikonomopoulos[3], Dunarel Badescu[3], Roy Dudley[2,4], Ioannis Ragoussis[3], Myriam Srour[2,4]

[1] Integrated Program in Neurosciences, McGill University, Montreal, Canada
[2] The Research Institute of the McGill University Health Centre, Montreal, Canada
[3] McGill Genome Centre, Montreal, Canada
[4] Department of Medicine, McGill University, Montreal, Canada

PhD Student-Senior

Focal cortical dysplasias (FCDs) are groups of abnormal disorganized neurons and glial cells in the cerebral cortex and represent the most common cause of drug-resistant epilepsy, accounting for ≈15-25% of cases. Somatic mutations in genes of the mTOR pathway are responsible for a subset of FCDs. These mutations are present in a small proportion of cells and result in mTOR hyperactivation. It remains unclear which cell type(s) within the genetically-heterogeneous FCD carry causal mutations. Also, it is puzzling how such a small proportion of mutated cells can result in such devastating epilepsy. Remarkably, single nuclei RNA sequencing (snRNA-seq) captures the RNA expression profile of individual cells and can provide valuable insight into the affected cell's lineage, identity, and function. Applying this technology to FCD can now unlock the cell type (s) that harbor FCD mutations and characterize the heterogeneous cell populations. The overarching goal of this project is performing snRNA-seq in genetically characterized FCD tissue to characterize mTOR-mutant cell populations within the FCD and non-mutated cells within the FCD. So, we will perform snRNA-seq in brain samples from the core of the FCD lesions as well as distant from the lesion in patients with identified causal mutations. Furthermore, we will determine which cellular subtypes carry the somatic mutations and whether these subpopulations arise from a common progenitor cell type. Detection of mTOR-dependent gene misregulation will be performed through a comparison of RNA-seq data between cell-type matched mutation-positive and negative cells. We will characterize the transcriptional profile of different mutation-negative cell types in proximity to and distant from mTOR mutant cells to determine the local effect of the mutant cells. The proposed study will lead to an improved understanding of the mechanisms underlying FCD pathophysiology, and identify novel potential therapeutic targets.

44- Ezhip Mediates Stalled Mesenchymal Development And Drives aggressive Osteosarcoma Tumorigenesis

Wajih Jawhar[1,2,3], Geoffroy Danieau[2], Alva Annett[3,4], Sungmi Jung[5], Anna Castillo Orozco[2,4], Liam Roberts[3], Nada Jabado[1,2,3,6], Livia Garzia[1,2,4,7]

[1] Department of Experimental Medicine, McGill University, Montreal, Quebec.
[2] Cancer Research Program, Research institute of the McGill University Health Center, Montreal, Quebec.
[3] Child Health and Human Development Program, Research institute of the McGill University Health Center. Montreal, Quebec.
[4] Department of Human Genetics, McGill University, Montreal, Quebec.
[5] Department of Pathology, McGill University Health Centre, Montreal, Quebec.
[6] Department of Pediatrics, McGill University, Montreal, Quebec.
[7] Department of Experimental Surgery, McGill University, Montreal, Quebec.

PhD Student-Senior

Introduction: The epigenetic landscape plays a key role in orchestrating spatio-temporal gene expression. This mechanism regulates dynamic processes such as lineage specification and normal development. Epigenetic aberrations have been identified as drivers of oncogenesis in a number of childhood malignancies. However, this has been poorly investigated in other cancers, such Osteosarcoma (OS), as it is believed that their vast genomic alterations are the main drivers of oncogenesis. OS peak of incidence coincides with the pubertal growth spurt during which cell proliferation and differentiation peaks in bone extremities. This led us to hypothesize that altered developmental programs have a key role in OS pathogenesis. Given the role of epigenetics and chromatin in development, we screened OS tumours for chromatin modifiers and discovered that a substantial percentage harbor ectopic expression of the newly identified oncohistone mimic ""EZHIP"".

Methods: The expression of oncohistones was evaluated by immunohistochemistry in a cohort of pediatric and adult Osteosarcomas. We correlated their expression with the abundance of the repressive histone mark H3K27me3 and investigated co-occurring mutations. Next, we studied the effect of EZHIP on the epigenome and transcriptome and its role in stalling mesenchymal development and OS pathogenesis. Finally, we assessed whether EZHIP confers resistance to chemotherapy using in-vitro drug assays.

Results: The overexpression of EZHIP in human and murine mesenchymal cells severely compromised their differentiation propensity and instead promoted a hyperproliferative phenotype. In OS lines, EZHIP expression drove signatures reminiscent of aggressive tumours and potentiated malignant behavior in vivo. While EZHIP expression enhances tumorigenicity, it also poses a window for therapeutic opportunity as EZHIP-expressing cells were found more vulnerable to epigenetic therapies.

Conclusion: We conclude that the EZHIP-mediated altered chromatin landscape may constitute a novel mechanism of OS pathogenesis. Strategies targeting such mechanisms should be considered in future treatment options for OS patients.

45- Delineating genotype-phenotype relationships in the extracellular matrix protein, COL4A1, as a novel monogenic cause of congenital anomalies of the kidney and urinary tract

Zachary Nurcombe[1,2], Zachary Sentell[1,2], Lina Mougharbel[2], Paul R. Goodyer[1,2,4] & Thomas Kitzler[1,2,3]

[1] Department of Human Genetics, McGill University, Montreal, Canada
[2] The Research Institute of the McGill University Health Centre, Montreal, Canada
[3] Division of Medical Genetics, McGill University Health Centre, Montreal, Canada
[4] Department of Pediatrics, McGill University Health Centre, Montreal, Canada

PhD Student-Senior

Congenital anomalies of the kidney and urinary tract (CAKUT) are the most common cause of chronic kidney disease in children. Whole-exome sequencing identified rare heterozygous variants in the Type IV Collagen alpha 1 gene (COL4A1) as a potential novel cause of CAKUT in children (Kitzler Hum Genet 2019).

Pathogenic variants in COL4A1 cause a broad spectrum of diseases, including eye defects, brain small vessel disease, and systemic defects; however, CAKUT were not reported. Notably, single-cell RNA-seq analysis shows early co-expression of COL4A1 with GATA3, an already established CAKUT gene (Tran Dev Cell 2019). Moreover, by use of gene-ontology terms through the PANTHER database, we demonstrated that genes regulating the collagen-containing extracellular matrix are statistically overrepresented among currently established CAKUT genes.

Collagens are expressed in the endoplasmic reticulum (ER) and secreted into the extra-cellular space to form heterotrimers. Proposed disease mechanisms for COL4A1 variants include monomer instability, abnormal heterotrimer formation, as well as ER-stress. We will study COL4A1 misfolding by analyzing protein localization, ER stress, and the use of a split-luciferase assay to determine heterotrimer formation and stability. We have completed cloning of expression constructs (untagged and GFP-tagged) for 10 patient-specific variants, to study the disease specific effects for each.

Next, we will recapitulate CAKUT in a zebrafish by knockdown and knockout of COL4A1. Zebrafish are an excellent model study the development of the kidney as they share many of the developmental structures and pathways with humans. The translucency of their skin allows for easy visualization of the underlying structures. Utilizing wholemount in situ hybridization to visualize the zebrafish urinary tract, we collected data that suggests that the knockdown of COL4A1 results in abnormal kidney development.

Finally, we will use the here developed cell and animal models to screen for novel drug targets for a disease where currently no treatment exists.

46- NICU Manager's Perception of Organizational Factors in the Neonatal Intensive Care Unit

Carla Herman[1], Elias Jabbour[1], Bruno Piedboeuf[2], Edith Masse[3], Victoria Bizgu[4], Shah Prakeshkumar[5], Joseph Ting[6], Marc Beltempo[1], On Behalf of the Canadian Neonatal Network

[1] McGill University, Montreal QC, Canada
[2] Centre Hospitalier Universitaire de Québec, Sainte Foy, Québec
[3] Centre Hospitalier Universitaire de Sherbrooke, Sherbrooke, Québec
[4] Jewish General Hospital, Montréal, Québec
[5] Mount Sinai Hospital, Toronto, Ontario
[6] University of Alberta Hospital Stollery Children's, Edmonton, Alberta

Medical Student-Junior

INTRODUCTION
Each year, 15,000 critically ill neonates require specialized care that is offered in only 32 tertiary neonatal intensive care units (NICUs) in Canada. Previous studies have shown associations between nurse-to-patient ratios and higher bed occupancy with patient outcomes. This study aimed to explore neonatal managers' perceptions of organizational factors in Canadian NICUs.

METHODS
This was a web-based cross-sectional survey, consisting of 20 questions on the determinants of resource allocation, the ascertainment of high occupancy state, as well as the different challenges and mitigation strategies. The survey was first piloted and validated before being distributed to the unit manager of all Canadian Level-3 NICUs between August and November 2022. The data was presented using descriptive statistics.

RESULTS
A total of 22 unit managers (69%) completed the survey. Most respondents relied on their clinical judgment to estimate the total number of nurses required per shift (50%) and the individual nurse-to-patient ratios (68%) as opposed to nursing workload assessment tools (9% and 0%, respectively). The most common organizational challenges were personnel retention and unit occupancy (reported as being a major issue by 41% and 36%, respectively, of respondents). Although most (77%) respondents believed that high occupancy, especially when exceeding 90%, likely increases the risk of adverse patient outcomes; they revealed implementing mitigation strategies to reduce occupancy only when it exceeded 95%. At that point, the most common strategies implemented were using voluntary nursing workforce and accelerating patient transfer.

CONCLUSION
Although NICUs across the country form a very heterogeneous group, managers shared similar perspectives in terms of staffing and occupancy challenges. This emphasizes the need for collaborative NICU person-power resource management practice to improve neonatal intensive care service organization.

47- Endometriosis, Chronic Pain, Anxiety, and Depression: A Retrospective Study Among 12 Million Women

Hormoz Nassiri Kigloo, MD[1*]; Rayan Itani, MD[1*]; Tina Montreuil, PhD[2]; Ido Feferkorn, MD[1]; Jason Raina, MD[1]; Togas Tulandi, MD, MHCM[1]; Fady Mansour, MD[1]; Srinivasan Krishnamurthy, MD; Eva Suarthana, MD, PhD[1]

[1]Department of Obstetrics and Gynecology; McGill University, Montréal, Québec, Canada
[2]Department of Psychiatry McGill University, Montréal, Québec, Canada
*Shared first-authorship

Research Assistant

Background: There is a lack of information regarding the impact of the physical symptoms associated with endometriosis and chronic pain on the mental well-being of affected women. Thus, our study aimed to evaluate the relationship between endometriosis, chronic pain, anxiety, and depression.

Objective: Our study aimed to evaluate the relationship between endometriosis, chronic pain, and mental health disorders among women registered in an extensive database until 2014.

Study design: This was a retrospective population-based study involving 12,904,324 hospitalized women from the Healthcare Cost and Utilization Project (HCUP) database between 2007 and 2014. We calculated the prevalence of chronic pain, endometriosis, anxiety, and depression during the study period. We used multivariate logistic regression to examine the relationship between these variables.

Results: An upward pattern was noted in the prevalence of chronic pain, while an opposite trend was seen for endometriosis during the study period. After adjusting for sociodemographic characteristics and comorbidities, including depression, the highest odds ratio of experiencing anxiety appeared in the group with both chronic pain and endometriosis (OR=2.962, 95% CI 2.706-3.243).

Limitations: HCUP is an administrative database that does not link patients' records over the years. Thus, it is difficult to establish any temporal association between endometriosis, chronic pain, anxiety, and depression.

Conclusion: Potential associations were identified between endometriosis, with and without chronic pain, anxiety, and depression. We recommended that clinicians provide proper medical management of endometriosis-related pain through symptom management and adequate counseling for those suffering from anxiety and depression.

48- The Effect of Maternal Hypertension and Maternal Mental Illness on Adverse Neonatal Outcomes: A Mediation and Moderation Analysis in 9 Million Pregnancies

Jason Raina, MD[1]; Guillaume Elgbeili, MSc[2]; Tina Montreuil, MD, OPQ[2]; Tuong-Vi Nguyen, MD, MSc[1,2]; Marc Beltempo, MD[3]; Dian Kusuma, MPH, ScD[4]; Togas Tulandi, MD, MHCM[1]; Natalie Dayan, MD, MSc[1]; Femmy Yunia Bahroen, MD, MHA1; Christina Caccese, MSc[5]; Ahmad Badageish, MD, MPH, FRCSC 1; Eva Suarthana, MD, PhD[1]

[1]Department of Obstetrics and Gynecology, McGill University, Montréal, Québec, Canada.
[2]Department of Psychiatry, McGill University, Montréal, Québec, Canada.
[3]Department of Pediatrics, McGill University, Montréal, Québec, Canada.
[4]Centre for Health Economics & Policy Innovation, Imperial College Business School, London, UK.
[5]McGill University Health Center, Montréal, Québec, Canada.

Research Assistant

While Hypertensive Disorders of Pregnancy (HDP) coexist with maternal anxiety and depression, it is unclear how these conditions affect neonatal outcomes. We evaluated the prevalence, associations, and potential mechanisms between HDP, maternal mental disorders, preterm birth, and small for gestational age (SGA).

We conducted a retrospective population-based study using the Healthcare Cost and Utilization Project (HCUP) database from 2004 to 2014. Preterm birth (<37 weeks), SGA (<10th percentile for gestational age and sex), HDP and mental disorders (anxiety and depression) were extracted using the International Classification of Diseases, Ninth Revision (ICD-9). Mediation and moderation models were separately constructed to evaluate potential mechanisms between maternal mental disorders, HDP, and adverse neonatal outcomes. Multivariate logistic regressions were used to determine their associations.

Of 9,097,355 pregnant women, the prevalence of HDP was 6.9%, anxiety 0.91%, depression 0.36%, preterm birth 7.2%, and SGA 2.1%. Anxiety increased the risk of HDP (OR=1.242, 95% CI 1.235–1.250), and HDP mediated the association between anxiety and preterm birth (mediation effect=0.048, p-value<0.001). Depression significantly moderated the effect of HDP on preterm birth (moderation effect=-0.126, p-value=0.027). HDP also mediated the association between anxiety and SGA (mediation effect=0.042, p-value<0.001), but depression did not moderate the association between HDP and SGA (p-value=0.29).

To conclude, our study suggests that women with anxiety had a greater risk of having HDP, and HDP mediated the associations between anxiety and adverse neonatal outcomes. Depression moderated associations between HDP and preterm birth, but not between HDP and SGA. We recommend early screening among pregnant women for anxiety and depression in the first trimester as early as possible to avoid downstream neonatal complications.

49- Placental methylome and transcriptome response to assisted reproduction: protective and sex-specific effects of moderate dose folic acid supplementation

Josée Martel[1], Rita Gloria Ihirwe[2], Sophia Rahimi[1] and Jacquetta Trasler[1,2,3,4]

[1] Research Institute of the McGill University Health Centre, Montreal, Quebec, Canada
[2] Department of Pharmacology & Therapeutics, McGill University, Montreal, Quebec, Canada
[3] Department of Human Genetics, McGill University, Montreal, Quebec, Canada
[4] Department of Pediatrics, McGill University, Montreal, Quebec, Canada

Research Staff

Assisted reproductive technologies (ART) have been associated with a higher incidence of adverse perinatal outcomes and epigenetic perturbations. Here, we hypothesize that ART perturbs the DNA methylome and transcriptome during early placenta development, leading to abnormal placental phenotypes observed in ART pregnancies at term. Folic acid (FA) is an essential methyl provider, and we propose that FA supplementation can rescue ART-induced placental defects. Female mice were placed on a control diet (CD), a moderate 4-fold (FAS4) or high dose 10-fold (FAS10) FA- supplemented diet prior to ART and compared to a natural mating group. ART perturbed the expression of 41 and 28 genes in E10.5 female and male placentas, respectively, and many of these were implicated in early placenta development and associated with DNA methylation (DNAme) changes. Alterations in female gene expression were partially corrected by FAS4 while FAS10 showed evidence of male-biased adverse effects. DNAme and gene expression for five genes involved in early placentation (Phlda2, EphB2, Igf2, Peg3, L3mbtl1) were followed up in placentas from normal as well as delayed and abnormal embryos. Placentas from female delayed embryos exhibited the lowest Phlda2 and Igf2 expression levels following ART. Furthermore, ART also reduced DNAme at the Kcnq1ot1 ICR regulating Phlda2 expression and FAS4 partially corrected this decrease in a sex-specific manner. In conclusion, ART-induced placental DNA methylome and transcriptional perturbations observed at mid-gestation are sex-specific; they may contribute to the adverse placental phenotypes observed at term and are partially corrected by maternal moderate dose FA supplementation. Funded by CIHR

50- Assessing the needs for a mobile app for individuals living remotely with pediatric-onset cancer predisposition syndromes

Leila Feng[1], Lara Reichman[1 2], Catherine Goudie[1 3]

[1] Department of Child Health and Human Development, Research Institute of the McGill University Health Centre, Montreal, Quebec, Canada.
[2] McGill University Health Centre, Department of Human Genetics, Montreal, Quebec, Canada.
[3] Division of Hematology-Oncology, Department of Pediatrics, McGill University Health Centre, Montreal, Quebec, Canada.

Research Staff

Background: Individuals living at an increased distance from their cancer screening centre experience differences in access to, and usage of, cancer screening services. Research has also found that mobile apps have the potential to improve healthcare access. The purpose of this study was to explore the experiences of caregivers of/patients with pediatric-onset cancer predisposition syndromes (CPSs) who are followed in a cancer surveillance clinic ≥20km from their home and ask them if/how a mobile app could help address barriers and improve their cancer screening care.

Methods: Eligible families were currently served by the MUHC cancer surveillance clinic and lived ≥20km from the MUHC. Opt-out recruitment was used. Study participation included a demographic questionnaire and a semi-structured interview asking about participants' feelings towards their CPS management, what barriers they experience towards their care, and what preferences they have for a hypothetical mobile app that could help them with their CPS management. Interview transcripts were studied using inductive thematic analysis.

Results: Four caregivers and two patients aged ≥18 years participated. Six themes emerged from the data: 1) There is a variety of challenges in the cancer screening experience; 2) The cancer screening experience is improved by the presence of accessible providers; 3) Care management should be a priority for the app; 4) There are multiple factors involved in app accessibility; 5) External resources that the app could offer would be beneficial overall, but opinions on specific resources are divided; and 6) The potential benefits of the app outweigh its potential concerns.

Conclusion: We conclude that caregivers of, and patients with, CPSs who live at an increased distance from their cancer screening centre face a variety of challenges in their CPS management, and feel that a mobile app could help them overcome these challenges and improve their overall cancer screening experience.

*The above results emerged from the first series of six participants, which was completed as part of graduation requirements for the presenting author. The presenting author has now graduated, but is continuing to work on this study and has recruited additional study participants, for which data analysis is ongoing. If that is completed in time before the conference, those additional findings (11 more participants) will also be presented.

51- Characterization of cell-specific mutational landscape of focal cortical dysplasia using single nucleus RNA sequencing

Lina Mougharbel[1], Spyros Oikonomopoulos[2], NassimaAddour[1], Dunarel Badescu[2], Roy Dudley[1,3], Jiannis Ragoussis[2], Myriam Srour[1,3]

[1] The Research Institute of the McGill University Health Centre, Montreal, Canada,
[2] McGill Genome Centre, Montreal, Canada,
[3] Department of Medicine, McGill University, Montreal, Canada

Research Staff

Background: Epilepsy is a common neurological disorder affecting 1% of the world population. Focal cortical dysplasias (FCDs) are small structural brain abnormalities composed of abnormal and disorganized cells that arise during fetal development. FCDs are the most common cause of medication-resistant epilepsy in children and adults. Surgical resection of FCDs is possible in a subset of patients. We've been collecting and screening fresh-frozen patient FCD tissues. Bulk-derived DNA screens identified somatic mTOR mutations in 14 FCD samples at 1-8% alternate allele frequency. Questions such as which cell-types within the FCD carry the somatic mutations remain unanswered.

Methods: We're using 10X Chromium Technology to perform single-nucleus RNA-seq in FCD samples. Because the mutations lie in the middle of cDNA molecules, we cannot rely on sequencing the 3'-ends to detect them. Therefore, following amplification from 10X full-length cDNA, we're enriching our target-gene then performing long-read sequencing of the full-length amplicons on a Nanopore platform (PremethION). Long-read sequencing data allows us to determine the mutational status, and short-read sequencing data allows us to identify the nuclei type and assign its mutational status.

Results: We successfully isolated nuclei, captured, and amplified a 10X full-length cDNA library from one FCD sample. We enriched our gene-of-interest using a biotin-tagged gene-specific primer and streptavidin beads followed by on-bead amplification and nested PCRs using two additional gene-specific primers. Over 10,000,000 high-quality full-length amplicons were sequenced, of which over 90% were on-target. We assigned the mutational status of 4,985 nuclei, of which 260 carried the mutation. We identified the cell type and gene-specific markers of these mutated cells.

Conclusion: Our novel approach, combing long-read and short-read sequencing data successfully allows us to identify the type and mutational status of individuals cells within the genetically heterogeneous FCD tissue. This is the first characterization of the cell-specific mutational landscape in FCD.

52- Zebrafish to the Rescue: Enabling Access to Novel Personalized Treatments for Children with Primary Ciliary Dyskinesia and Unresolved Genetic Testing

Lina Mougharbel[1], Zachary Nurcombe[1,2], Adam Shapiro[1,3], Thomas Kitzler[1,2,4]

[1] The Research Institute of the McGill University Health Centre, Montreal, Canada
[2] Department of Human Genetics, McGill University, Montreal, Canada
[3] Department of Pediatrics, McGill University Health Centre, Montreal, Canada
[4] Division of Medical Genetics, McGill University Health Centre, Montreal, Canada

Research Staff

Background: Primary ciliary dyskinesia (PCD) is a rare genetic disease causing chronic oto-sino-pulmonary infections with bronchiectasis. Genetic testing is the diagnostic mainstay for PCD, but in 20-30% of cases, the diagnosis cannot be confirmed due to variants of uncertain significance in known PCD genes. Molecular confirmation is paramount for timely treatment initiation with improved outcomes but is a sine qua non for clinical application of developing personalized inhaled mRNA treatments. Hence, there is a pressing need for clinical validation tests for unresolved PCD variants.

Aim: In collaboration with Dr. Adam Shapiro, the Kitzler Lab proposes the Zebrafish Variant Resolution (ZeVaR) Program for children with suspected but genetically unconfirmed PCD. This program uses zebrafish larvae for validation of VUS pathogenicity in PCD genes.

Hypothesis: Knockdown and rescue of PCD genes in zebrafish will recapitulate the human PCD phenotype to validate patient-specific VUS as disease-causing.

Methods: We will use morpholino oligonucleotide PCD gene knock-down for detailed phenotype characterization in zebrafish larvae. Once gene-specific phenotype read-outs are established, rescue experiments with human patient-specific mRNA will establish variant pathogenicity. Once validated, workflow per variant readout should take around three weeks, allowing for rapid validation in a clinical setting.

Impact: This proof-of-concept study for rapid genetic variant validation in patients with suspected PCD aims to enable access to future personalized therapies for patients with unresolved genetic testing. Moreover, the developed animal models will be used to characterize less well-defined cellular components involved in various PCD phenotypes, identify novel PCD candidate genes, and will eventually allow screening for novel targeted PCD therapies in the future.

53- Composite Neonatal Adverse Outcome Indicator for Preterm Infants – A Population-based Study in Canada

Satit Manopunya[1], Marc Beltempo[1], Xiang Y. Ye[2], Prakash Shah[3].

[1] McGill University, Montreal, Canada
[2] Maternal-infant Care Research Center, Mount-Sinai Hospital, Toronto, Canada
[3] Mount-Sinai Hospital, University of Toronto, Toronto, Canada

Principal Investigator

Background: Neonatal adverse outcome indicators derived from hospital discharge data are used for comparing the quality of perinatal and neonatal care worldwide but are not specific for preterm infants.

Objective: To define and evaluate the incidence of composite neonatal adverse outcome indicators for preterm infants (P-NAOIs) in Canada, and to assess its associations and predictive abilities with 2-year outcomes among those discharged alive.

Methods: We conducted a population-based study of preterm infants born 24-36 weeks gestation age (GA) in Canada from April 2010 to March 2015. Diagnostics and procedural components of P-NAOI were selected and identified by using the Canadian Institute for Health Information database. The incidence of P-NAOI and each component were evaluated. The associations and predictive abilities of 4 different P-NAOI definitions: classic, modified, diagnostic, and procedural P-NAOI with 2-year mortality and/ or hospital readmission among NICU survivors were determined. The provincial incidence rate of each P-NAOI and its standardized ratio adjusted for sex, gestational age, singleton, small for gestation age, and mode of delivery across Canada were compared.

Result: The incidence of classic, modified, diagnostic, and procedural P-NAOI among 166,484 eligible infants born at 24-36 weeks GA were 34.8%, 33.7%, 21.1% and 28.%, respectively. Among the 165,362 NICU survivors 18,677 (11.2%) either died and/or readmitted within 2 years. Even though all four P-NAOIs were associated with 2-year mortality and hospital readmission (Table 3), the diagnostic P-NAOI provided the strongest association (RR, 95% CI = 1.44, 1.39-1.48). However, its accuracy for predicting the 2-year outcome was low (AUC, 95% CI = 0.53, 0.53-0.54). When comparing the regional incidences of classic, modified, and diagnostic P-NAOI across Canada, there were significant variations in provincial rates, suggesting an opportunity for improvement.

Conclusion: The diagnostic P-NAOI could be used as an indicator for benchmarking the quality of neonatal care for preterm infants.

54- Maternal characteristics and regional organizational factors associated with outborn delivery of infants <32 weeks

Satit Manopunya[1], Sharina Patel[1,2], Bruno Piedboeuf[3], Christine Drolet[3], Anie Lapointe[4], Victoria Bizgu[5], Edith Messe[6], Marc Beltempo[1]

[1] McGill University, Montreal, Canada
[2] McGill University Health Research Institute, Montreal, Canada
[3] Center Hospitalier Universitaire de Quebec, Quebec , Canada
[4] Center Hospitalier Universitaire de Montreal, Saint-Justine Hospital, Montreal, Canada
[5] Jewish General Hospital, Montreal, Canada
Maternal-infant Care Research Center, Mount-Sinai Hospital, Toronto, Canada
[6] Center Hospitalier Universitaire de
Sherbrooke, Sherbrooke, Canada

Principal Investigator

Background: Preterm infants <32 weeks gestational age (GA) born in hospitals without level 3 NICU (outborn) are at higher risk of adverse outcomes. A better understanding of risk factors related to outborn birth may help develop strategies to minimize outborn deliveries.

Objectives: To identify maternal and organizational risk factors associated with outborn deliveries among preterm infants born <32 weeks GA.

Methods: This retrospective cohort study included infants born at 23-31 weeks GA and admitted to all five Quebec's NICUs participating in the Canadian Neonatal Network (CNN) from 2014 to 2018. Regional organizational factors included geographic distance to closest Level 3 units and unit occupancy on Level 2 and 3 NICUs. The risk factors for outborn deliveries were evaluated using logistic regression analysis.

Result: There were 2874 eligible infants corresponding to 2494 pregnancies of whom 314 (12.5%) delivered outborn (341 infants). Maternal characteristics associated with higher odds of outborn delivery were teenage pregnancy (adjusted odds ratio (aOR) 3.45, 95% confidence interval (CI) 1.35-8.09) and spontaneous labour initiation (aOR 1.87, 95% CI 1.31-2.72). Geographic factors associated with higher odds of outborn delivery included longer travel time to the closest level 3 NICUs 30-60 minutes (aOR 1.48, 95% CI 1.01-2.15). Overall median regional and provincial unit occupancy in Level 2 and Level 3 NICUs on the day prior and day of outborn birth were either similar or lower for the outborn group.

Conclusion: We identified clinical risk factors for outborn preterm birth and patients at further distance from Level 3 units are at higher risk of outborn delivery. In our highly regionalized healthcare system, occupancy is not a barrier to access to care. However, 43% (137/314) of outborn infants lived within 32 km of Level 3 NICUs which suggests place for improvement in referral patterns for women at risk of very preterm delivery.

Evaluation forms will be provided to Judges in print on this page