From Gametes to Adulthood: Focus on Child Health and Human Development Research for Healthier Futures

May 9th, 2025

Research Day Booklet

Child Health and Human Development Program

Centre universitaire de santé McGill
Institut de recherche

McGill University Health Centre
Research Institute

Welcome to the 10th Annual

Child Health and Human Development Research Day

Word from the Child Health and Human Development Program

Dear colleagues and friends of the Child Health and Human Development Program,

It is with immense pleasure and honor that we welcome you to the 10th Edition of our CHHD Research Day where we celebrate and showcase the outstanding research conducted by our trainees and research staff. Such events are crucial for fostering collaboration, sharing knowledge, and advancing research. It is truly inspiring to witness the CHHD community's dedication to expanding the frontiers of knowledge. The diversity and quality of abstracts received this year underscores the excellence within our community.

We are particularly delighted to extend a warm welcome to **Dr. Elin Grundberg** from the University of Missouri-Kansas City School of Medicine. Her expertise and contributions to genomic research have significantly enriched the field of child health development. We are privileged to have her as our keynote speaker and eager to anticipate her insights into the epigenetics applied to perinatal and pediatric translational medicine studies.

Our deepest gratitude goes out to all participants, judges, volunteers, and sponsors. Your support and dedication have been instrumental in making this event a success. Your contributions are invaluable and exemplify the collaborative spirit that defines the CHHD community.

The Child Health and Human Development Program

Dr. Marie Brossard-Racine, Program Co-Leader
Dr. Loydie Majewska, Program Co-Leader
Dr. Isabelle Gagnon, Former Program Co-Leader
Dr. Kolja Eppert, Former Program Co-Leader
Fanny Toussaint, Program Manager
Angela Roussos, Program Assistant
Rosanna Camarda, Program Assistant
Sara Beydoun, Coordinator

AGENDA

No coffee allowed in the Cruess Amphitheater. Only clear water bottles with cap.

8:15 - 8:45	**REGISTRATION & POSTER SET UP**
	McConnell Atrium *Coffee and Pastries will be offered*
8:45 - 9:45	**Poster session 1 (odd numbers)**
	Evaluation for the presenters starts at 8:45. Please remain next to your poster for the whole session
9:55 - 10:05	**Welcoming remarks**
	Cruess Amphitheatre
10:05 - 11:05	**External Keynote Speaker**
	Dr. Elin Grudberg, PhD, University of Missouri-Kansas City School of Medicine *Title: Complete placental genome sequencing: functional signatures and developmental determinants of disease*
11:05 - 11:45	**Junior oral presentations**
	#1 to 4
11:45 - 13:00	**Lunch & Coffee**
	McConnell Atrium *Coupon required*
12:00 - 13:00	**Poster session 2 (even numbers)**
	Evaluation for the presenters starts at 12:00. Please remain next to your poster for the whole session
13:10 - 14:10	**Internal Keynote Speaker**
	Cruess Amphitheatre *Dr. Brett Burstein, MD, PhD, MPH, FRCPC, FAAP, McGill University, CHHD Scientist* *Title: Emergency Evaluation of Fever in Newborns: Integrating Quality Improvement, Patient Experience and Research to Change Dogma*
14:10 – 14:50	**Senior oral presentations**
	#5 to 8
15:00 - 15:15	**Winners announcement and closing remarks**
	Cruess Amphitheatre
15:15	**End of the event**

KEYNOTE SPEAKERS

External Keynote Speaker

Elin Grundberg, PhD
Professor in Pediatrics, University of Missouri-Kansas City School of Medicine
Roberta D. Harding & William F. Bradley, Jr. Endowed Chair in Genomic Research

Originally from Sweden, Dr. Elin Grundberg trained in Human Genetics at the Wellcome Trust Sanger Institute, Cambridge UK and at McGill University, Montreal, Canada. In 2012 she joined the faculty of McGill University in Montreal, Canada as a tenured-track Assistant Professor in Human Genetics and held between 2013-2017 the Canada Research Chair in Disease Genomics and Epigenomics. In 2017, Dr Grundberg was recruited to Children's Mercy Kansas City to establish epigenomics and single-cell programs for perinatal and pediatric translational medicine studies. She holds the Roberta D. Harding & William F. Bradley, Jr. Endowed Chair in Genomic Research and is a Professor in Pediatrics at UMKC School of Medicine. Her group is using latest sequencing approaches to pregnancy and pediatric samples to understand genetic and non-genetic (epigenetic) factors underlying disease risk. Her recent effort includes mapping parent-of-origin methylation pattern in early placental samples using long-read sequencing approaches unraveling novel imprinting signatures and related disorders

Internal Keynote Speaker

Brett Burstein, MD, PhD, MPH, FRCPC, FAAP
Scientist, CHHD
Associate Professor, Department of Pediatrics, Faculty of Medicine and Health Sciences, McGill University
Clinician-Scientist, Pediatric Emergency Medicine
Montreal Children's Hospital, MUHC

Dr. Brett Burstein received his M.D/Ph.D degrees from McGill University (2010) and MPH from Harvard (2018). He trained in General Pediatrics (2013) then Pediatric Emergency Medicine (2015) at the Montreal Children's Hospital, and was subsequently appointed as Clinician-Scientist at the McGill University Health Centre Research Institute. He serves on the Executive Committee of the Pediatric Emergency Research Canada (PERC) consortium, the Board of Directors for the Translating Emergency Knowledge for Kids (TREKK) network, the Research Committee of the Canadian Association of Emergency Physicians (CAEP), and is a Decision Editor for the Canadian Journal of Emergency Medicine. He holds a Clinical Research Scholar career award (FRQ-S), and has authored over 70 peer-reviewed articles, commentaries and book chapters with nearly 6000 career citations. His primary research interest is the emergency management of fever among infants in the first months of life, and he is the principal author of national guidelines from the Canadian Pediatric Society.

AWARDS

Good luck to all presenters!

Best junior oral presentation: 200$

Best senior oral presentation: 200$

Junior poster presentations:

First position: 150$

Second position: 125$

Third position: 100$

Senior posters presentation:

First position: 150$

Second position: 125$

Third position: 100$

The term "Junior" refers to: Medical student, Undergraduate student, MSc student
The term "Senior" refers to: PhD student, Post-Doc, Research fellow
Only poster and oral presentations by trainees will be considered for awards.

ABSTRACTS

Abstract 1 to 8: Oral presentations
Abstract 9 to 68: Poster presentations
(odd numbers: poster session 1 & even numbers: poster session 2)

MSc - Junior

1 - Interprofessional Collaboration in Perinatal Care: Nurturing Families with Complex Health and Social Needs at La Maison Bleue

Kyla Christianson[1], Christina Clausen[1], Lisa Merry[2], Marie-Christine Harguindeguy-Lincourt[3], Andraea Van Hulst[1]

[1]McGill University, [2]University of Montreal, [3]La Maison Bleue

Background: Interprofessional collaboration (IPC) involving various healthcare professionals working together to achieve optimal health in maternity care services has been shown to improve health outcomes, particularly in populations in contexts of vulnerability. La Maison Bleue (LMB), a community-based non-profit organization, delivers maternity care through a unique IPC model. We aimed to explore perceptions, barriers and facilitators to IPC and related competencies among healthcare providers providing maternal childcare at LMB. **Methods:** A sequential explanatory mixed-methods design was used (quant → QUAL) to provide a deeper understanding of IPC at LMB. First, participants (nurses, physicians and midwives) completed a survey assessing perceptions of IPC using a validated tool (n=12). Second, individual interviews were done with purposefully selected participants from stage 1 (n=8). IPC perception scores and qualitative interview data were analyzed and presented using a score-by-theme approach. **Results:** Survey findings and interviews revealed positive perceptions of IPC at LMB. Quantitative data showed that providers perceived organizational culture (IPC is prioritized at LMB), motivation (providers are committed to their work), and group social support (providers feel supported and appreciated by their team members) as most positively influencing IPC. Interview findings focused on four main themes: All in this together: how team members support each other to meet complex health and social needs; All under one roof: how communication strengthens interprofessional care; Walking alongside families: how providers accompany families together to meet their needs; and Finding the right fit: how providers define, adapt and integrate roles over time. Recommendations for advancing IPC at LMB included coordinators developing clearer role guidelines and increasing frequency of meetings across sites. **Conclusion:** Findings provides practical insights on perceptions of providers on IPC, its competencies, barriers and facilitators. These can strengthen the current IPC practice at LMB and inform other IPC based models of maternity care for women living in contexts of vulnerability.

2 - Dexamethasone's impact on lung ultrasound scores in extremely preterm infants with evolving bronchopulmonary dysplasia

Joshua Hazan Mea[1], Phoenix Plessas-Azurduy[1], Thomas Sonea[2], Pasinee Kanaprach[3], Carolina Michel Macías[4], Shiran Sara Moore[5], Punnanee Wutthigate[6], Jessica Simoneau[3], Daniela Villegas Martinez[3], Andréanne Villeneuve[7], Anie Lapointe[7], Guilherme Sant'Anna[3], Gabriel Altit[3]

[1]Division of Neonatology, Faculty of Medicine and Health Sciences, McGill University, Montreal, QC, Canada., [2]Faculty of Medicine, Université de Montréal, Montreal, QC, Canada, [3]Division of Neonatology, Department of Pediatrics, Montreal Children's Hospital, Montreal, QC, Canada, [4]Faculty of Medicine, Universidad Autónoma de Querétaro, Querétaro, Mexico, [5]Division of Neonatology, Department of Pediatrics, Dana Dwek Children's Hospital, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel, [6]Department of Pediatrics, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand, [7]Division of Neonatology, Department of Pediatrics, CHU Sainte-Justine, Université de Montréal, QC, Canada

Background/Hypothesis: Bronchopulmonary dysplasia (BPD) is a common complication in premature infants, often linked to prolonged mechanical ventilation. Dexamethasone (DEXA) is used in these neonates to reduce pulmonary inflammation and facilitate the transition to non-invasive respiratory support. Lung ultrasound (LUS) can assess lung parenchymal changes, particularly variations in density related to atelectasis and inflammation. We hypothesize that LUS scores will decline following DEXA administration in preterm infants with evolving BPD.

Materials and Methods: This prospective observational study enrolled preterm infants born at <29 weeks gestational age (GA) who received DEXA for evolving lung disease. LUS was performed at DEXA initiation, days 3, 7, and 14 of treatment, 1 and 2 weeks post-treatment, and at 36 weeks corrected GA. Each of the six lung regions was scored by a blinded reviewer from 0 to 3, with a maximum possible score of 18 indicating greater consolidation.

Results: From 2021 to 2024, 38 neonates were recruited (61% male, 79% inborn), with 81% developing moderate-to-severe BPD as per the Canadian Neonatal Network. Three patients died (8%). The mean GA at birth was 25.4 weeks (SD: 1.4), and the mean birthweight was 757g (SD: 192g). Median Apgar scores were 6 (IQR: 5-7) and 8 (IQR: 6-8) at 5 and 10 minutes, respectively. Among survivors, the average hospitalization duration was 134 days (SD: 47). A mixed-effects model demonstrated a significant decline in average LUS score ($\beta = -0.54$, 95% CI: -0.67 to -0.40, $p < 0.001$) and in percentage scores ($\beta = -3.0$, 95% CI: -3.7 to -2.2, $p < 0.00001$) during DEXA treatment. The decline began with DEXA exposure and continued without rebound after cessation, with the lowest values observed at 36 weeks corrected GA.

Conclusions: DEXA treatment was associated with a sustained reduction in LUS scores, suggesting improved aeration, with benefits lasting beyond treatment cessation.

3 - High-Fat Diet Induces Gut Microbiome Dysbiosis and Impairs Sperm Quality in Mice

Melody Pan[1, 2], Eleonora Scarlata[2], Fiona Hui[3], Jianguo Xia[3], Cristian O'Flaherty[1, 2]

[1]Department of Pharmacology and Therapeutics, McGill University, [2]Department of Surgery (Urology Division), McGill University, [3]Department of Parasitology, McGill University

Infertility affects one in six couples worldwide, with male infertility contributing to ~50% of all cases. Obesity is rising globally and is highly prevalent in infertile men, suggesting an association of obesity with male infertility. Emerging evidence further links gut microbiota dysbiosis with male infertility; however, the mechanisms underlying the existence of a gut-testis axis remain unclear. We hypothesize that high-fat diet (HFD)-induced gut microbiome dysbiosis promotes male infertility through abnormal metabolic products in male mice. Our objectives were to: 1) compare the gut microbiome signatures in HFD-fed and normal diet (ND)-fed male mice and 2) determine HFD effects on spermatogenesis, epididymal maturation and sperm quality. C57BL6 male mice were fed a 45% fat diet (HFD, n=38) or a 10% fat diet (ND, n=39) from 3 to 8 weeks of age. Fecal samples were collected for 16S rRNA sequencing. Testis samples were analyzed for acrosome biogenesis using Periodic acid-Schiff staining. Cauda epididymis spermatozoa were assessed for sperm motility and cytoplasmic droplet retention using a CASA system. Sperm acrosomal integrity, lipid peroxidation and DNA oxidation were evaluated by Giemsa staining or immunocytochemistry. Microbiome sequencing data were analyzed using MicrobiomeAnalyst 2.0. HFD-fed mice showed reduced sperm motility and velocity parameters, increased acrosomal damage, oxidative stress and abnormal epididymal maturation. HFD-fed mice had increased Firmicute/Bacteroidota ratio, Lachnospiraceae, Peptococcaceae, Oscillospiraceae, Staphylococcaceae, Erysipelatoclostridiaceae and Akkermansiaceae, and a decrease in Muribaculaceae. The reduction in Bacteroidota, specifically Muribaculaceae, is associated with inflammation and decreased production of short-chain fatty acids, negatively affecting gut health and overall metabolism. Increased abundance of Lachnospiriaceae is associated with obesity and metabolic syndrome. Increased abundance of Erysipelotrichaceae has been observed in host metabolic disorders and inflammatory diseases. The treatment established an oxidative stress impairing sperm quality and function leading to male infertility. Supported by a MI4 grant and the Pathy Family Foundation.

4 - Developing a biotin ligase proximity assay to characterize the Claudin-3 interactome in chick embryos.

Zafina Budhwani[1, 2], Aimee Ryan[1, 2]

[1]Department of Human Genetics, McGill, [2]Child Health and Human Development

Neural tube defects are birth abnormalities that result from the improper closure of the neural tube, the precursor to the brain and spinal cord. Improper closure can lead to malformations in the brain or spinal cord, such as spina bifida. Our lab discovered that Claudin-3, a tight junction protein, plays a critical role in neural tube closure. However, the molecular mechanism by which Claudin-3 directs neural tube closure is unknown. My goal is to adapt a BioID method to detect and characterize Claudin-3 protein interactions in chick embryos in order to identify possible downstream effectors of Claudin-3 in neural tube closure. Biotin ligase proximity assays use a promiscuous biotin ligase fused to a protein of interest to biotinylate and identify proteins near the protein of interest. In this project we have engineered a modified biotin ligase, TurboID fused in frame to the N-terminus of Claudin-3. In HEK293 cells we have optimized TurboID::Claudin-3 fusion protein expression. Through immunofluorescence experiments we have shown that TurboID::Claudin-3 localizes to the cellular membrane. We have also shown that TurboID is functionally active and able to biotinylate proteins after addition of exogenous biotin to cell media. To further show functionality, biotin-tagged proteins will be purified using Streptavidin agarose beads and purified lysates will be probed with known interactors of Claudin-3 such as ZO-1. After initial optimization in cells, we will apply our method to developing chick embryos to better understand spatial and temporal protein interactions of Claudin-3 during neural tube closure. Although this technique has been done in other species, to our knowledge this will be the first time it is being used in live chicken embryos. The ultimate goal of this project will be to identify the molecular mechanisms of neural tube closure that depend on Claudin-3 and its interaction partners.

Research/Medical fellow

5 - Polycystic Ovary Syndrome and Severe Maternal Morbidity: Population-based cohort study

Maria A. Hincapie[1], Joel G. Ray[2, 3], Jonas Shellenberger[2], Maria P. Velez[1, 2, 4]

[1]McGill University Health Centre Reproductive Centre, [2]ICES, Toronto, Canada, [3]Department of Medicine, University of Toronto, Toronto, Canada, [4]Research Institute McGill University Health Centre

Objective: To evaluate whether a pre-existing diagnosis of polycystic ovary syndrome (PCOS) is associated with an increased risk of severe maternal morbidity (SMM).

Background: Women with PCOS face a higher risk of pregnancy complications, including preterm delivery, hypertensive disorders, gestational diabetes, and cesarean delivery. Metabolic conditions prevalent in PCOS—such as insulin resistance, obesity, and chronic hypertension—are established risk factors for adverse pregnancy outcomes. However, limited data exist on the relationship between PCOS and SMM, a validated composite outcome occurring during pregnancy or within 42 days postpartum.

Study Design, Size, Duration: This population-based cohort study analyzed all births in Ontario, Canada, between October 2006 and February 2021. A total of 492,147 pregnancies in women with PCOS and 1,104,081 pregnancies in women without PCOS were included. PCOS diagnoses were identified using ICD-9 codes, and SMM was classified as likely related or unrelated to PCOS.

Methods: A modified Poisson regression model was used to estimate the relative risk (RR) of SMM in women with and without PCOS, adjusted for maternal age, parity, income quintile, rurality, obesity, and smoking status. The study also stratified results by pregnancy characteristics and mode of conception, including ovulation induction (OI), intrauterine insemination (IUI), and in vitro fertilization (IVF).

Results: Women with PCOS had a modestly increased risk of SMM compared to those without PCOS (20.8 vs. 19.1 per 1000 births), with an adjusted RR of 1.07 (95% CI 1.04-1.09). The risk was higher for PCOS-related SMM (adjusted RR 1.12, 95% CI 1.08-1.16). Among women with PCOS and chronic hypertension, the adjusted RR for SMM was 1.23 (95% CI 1.09-1.40). SMM risk varied by mode of conception, with a slight increase in unassisted conception (adjusted RR 1.05, 95% CI 1.02-1.08) and in women with infertility who did not undergo fertility treatment (adjusted RR 1.10, 95% CI 1.04-1.16). No significant increase was observed among those who conceived through OI/IUI or IVF.

Conclusions: Pre-existing PCOS is modestly associated with an increased risk of SMM, independent of obesity or fertility treatment. These findings highlight the importance of incorporating PCOS status into maternal risk assessments to guide clinical decision-making.

PhD – Senior

6 - Longitudinal Changes in Fractional Anisotropy in Neonates with Hypoxic-Ischemic Encephalopathy: Effects of Therapeutic Hypothermia and Sildenafil

Maria Jose Castro Gomez[1], Hossein Jomhle[1], Emmanouil Rampakakis[2], Gabriel Altit[1, 3], Anie Lapointe[4], Guillaume Gilbert[5], Robin Steinhorn[6], Walter E. Haefeli[7], Pia Wintermark[1, 3]

[1]Research Institute of the McGill University Health Centre, McGill University, Montreal QC, Canada, [2]Medical Affairs, JSS Medical Researchm Montreal QC, Canada, [3]Division of Newborn Medicine, Department of Pediatrics, Montreal Children's Hospital, McGill University, Montreal, Canada, [4]Division of Newborn Medicine, Department of Pediatrics, CHU Ste-Justine, University of Montreal, Montreal, Canada, [5]MR Clinical Science, Philips Healthcare, Montreal QC, Canada, [6]Department of Pediatrics, University of California San Diego, and Rady's Children's Hospital, CA, USA, [7]Department of Clinical Pharmacology and Pharmacoepidemiology, Heidelberg University Hospital, Heidelberg, Germany

Hypoxic ischemic encephalopathy (HIE) can lead to brain injuries and neurodevelopmental impairments. While therapeutic hypothermia (TH) is the standard treatment, up to 29% of treated neonates still suffer brain injury. Sildenafil (Viagra®) is a potential therapy with neuroprotective properties. This study uses diffusion tensor imaging (DTI) to assess fractional anisotropy (FA) changes in healthy neonates and those with HIE undergoing hypothermia +/- sildenafil treatment. Prospective study of healthy neonates (NoBI) and neonates with HIE treated with TH (BI+TH). Several BI+TH neonates received enterally administered sildenafil for 7 days. Brain MRIs were conducted around days 2, 10, and 30 of life. FA was calculated for six regions of interest (ROIs) and analyzed using repeated measures generalized linear models for each ROI. A total of 126 participants, 8 healthy neonates, 63 NoBI, 34 BI+TH, and 20 BI+TH/S, were scanned during the first month of life. On DOL 02, FA values were not different between the groups. By DOL 10 and 30, FA values were significantly decreased in BI+TH in all ROIs (thalamus, PLIC, posterior and anterior white matter [AWM/PWM], splenium, genu). In the BI+TH/S, FA values were not significantly different from those NoBI for some ROIs starting by DOL 10 (thalamus, PLIC, PWM and splenium) and for all ROIS by DOL 30. The BI+TH/S neonates displayed significantly increased FA values compared to BI+TH in two ROIs (thalamus, PLIC) by day 10 and in four ROIs (thalamus, PLIC, AWM, PWM) by DOL 30. Sildenafil treatment in addition to TH appeared to prevent/repair some of the microstructural impairments.

PhD – Senior

7 - Physiological and pathological Nodal-deficient pregnancies: single-cell characterization of leukocytes at the maternal-fetal interface

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

[1]Division of Experimental Medicine, McGill University, [2]Child Health and Human Development Program, RI-MUHC, [3]Department of Obstetrics and Gynecology, MUHC

Introduction: Leukocytes at the maternal-fetal interface have critical functions during pregnancy to prevent maternal reactivity towards fetal alloantigens, suppress excess inflammation and promote placental angiogenesis. Failed maternal immune adaptations to pregnancy can lead to placental insufficiency and many associated reproductive pathologies. Recently, the morphogen Nodal, from the TGFβ family, has been shown to act as an immunoregulator of pregnancy. Its deletion in the reproductive tract ($Nodal^{D/D}$) led to the loss of preimplantation regulatory T cells, a 50% implantation failure rate and placental dysfunction at mid-gestation. **As leukocytes have an emerging role in pregnancy complications, we hypothesize $Nodal^{D/D}$ model represents a unique system to study immune-mediated reproductive failure.**

Methods and Results: Single-cell RNA-sequencing was used to characterize leukocytes within the mid-gestational decidua and placenta in physiological and pathological $Nodal^{D/D}$ pregnancies. Eleven distinct immune cell clusters were identified, with a particular emphasis on characterizing unique and unknown macrophage and neutrophil subpopulations. Placenta-associated maternal macrophages were characterized for the first time in the mid-gestational mouse, with novel functions proposed in the regulation of angiogenesis, immune suppression and endocytosis. The differential abundance and expression profile of these leukocytes in $Nodal^{D/D}$ females closely replicated immune dysfunction observed in human pathologies.

Discussion: As failed maternal immune adaptations are associated with reproductive pathologies, better characterization of the mechanisms implicated could improve knowledge and treatment for pregnancy loss, preeclampsia and intrauterine growth restriction- three phenotypes observed in the $Nodal^{D/D}$ model. Together, elucidating the role of leukocytes during placental development provides a basis for future translational research, with the overall goal of improving pregnancy success and maternal and fetal health.

Post-doc - Senior

8 - The effect of partial sleep deprivation on cognitive performance in children with focal epilepsy

Katharina Schiller[1], Kassem Jaber[2], Saoussen Berrahmoune[3], Christelle Dassi[3], Birgit Frauscher[2], Kenneth Myers[1]

[1]Division of Neurology, Department of Pediatrics, Montreal, [2]Montreal Neurological Hospital, [3]Child Health and Human Development, Research Institute of the McGill University Health Centre, Montreal, Quebec, Canada

Background: Neuropsychological assessment is one element of presurgical evaluation in children with drug-resistant focal epilepsy. In clinical practice, patients are often partially sleep deprived while admitted to hospital with the aim of provoking seizures. However, the impact of sleep deprivation on performance on neuropsychological assessment is not known. Therefore, we aimed to study differences in cognitive performance after a normal sleep night compared to a night with partial sleep deprivation in children with focal epilepsy.

Methods: Six children with drug-resistant focal epilepsy (12.2 1.7 years, 3 female) underwent two 24-hour home ambulatory EEG with subsequent neuropsychological testing, one after a night with partial sleep deprivation (4 hours) and a second after a normal sleep night. The two EEGs were separated by at least three months. Neuropsychological assessment included the administration of standardized tests for attention, verbal memory (immediate and delayed recall) and spatial memory (immediate and delayed recall).

Results: Attention performance was significantly decreased under the condition of sleep deprivation compared to the normal night of sleep (Attention performance d2: 106.2 50.0 vs 127.2 32.3, p=0.039, d=0.90). Regarding verbal memory performance, there was a trend with a strong effect size of reduced performance at delayed recall under partial sleep deprivation compared to the normal sleep night (Correct pairs: 7.5 2.8 vs 9.5 2.8, p=0.13, d=0.73). In contrast, there was no difference between the delayed recall performances when sleep deprived compared to normal sleep in the spatial memory task (Correct pairs: 8.2 2.2 vs 8.6 2.3, p=0.60, d=0.23).

Discussion: There are differences in the neuropsychological performance in children with focal epilepsy after partial sleep deprivation compared to a normal night of sleep. This suggests that neuropsychological assessment should be scheduled outside of presurgical evaluation at the epilepsy monitoring unit to avoid potential confounding.

Undergraduate student - Junior

9 - Understanding the Interplay of Prenatal Health and Social Factors in Early Child Socio-Emotional and Behavioural Development

Laura Humez[1], Guillaume Elgbeili[2], Marion Lecorguillé[1, 3], Tina Montreuil[1, 3, 4, 5]

[1]Department of Educational and Counselling Psychology, Faculty of Education, McGill University, Montreal, QC, Canada., [2]Douglas Research Centre, Montreal, QC, Canada., [3]Research Institute of the McGill University Health Centre, Montreal, QC, Canada., [4]Department of Psychiatry, Faculty of Medicine and Health Sciences, McGill University, Montreal, QC, Canada, [5]Department of Pediatrics, Faculty of Medicine and Health Sciences, McGill University, Montreal, QC, Canada.

Introduction: The Developmental Origins of Health and Disease (DOHaD) hypothesis emphasizes the importance of prenatal factors in shaping long-term child development. Maternal health (including poor sleep, stress, anxiety, and depression) and social factors (such as low socioeconomic status (SES) and poor relationship quality) have been linked to adverse socioemotional and behavioural development, yet their interplay remains understudied. This study examines how key prenatal factors influence socioemotional and behavioural outcomes in children aged 18 to 36 months.

Methods: We used data from the Montreal Antenatal Well-Being Study, a longitudinal cohort of 1,130 mother-child pairs. Using Structural Equation Modeling, we grouped 11 maternal prenatal predictors of child development into four latent variables: (1) SES, (2) Maternal mental health, (3) Relationship quality, and (4) Sleep quality. We examined the associations between each latent factor and child socioemotional and behavioural outcomes assessed at 18 and 36 months using the Early Childhood Behaviour Questionnaire (Negative Affectivity, Surgency/Extraversion, Effortful Control) and the Child Behavior Checklist Preschool (Internalizing and Externalizing Symptoms).

Results: Preliminary analyses revealed significant associations between SES, relationship quality, and the Effortful Control (EC) subscale of the ECBQ (reflecting self-regulation of attention, emotions, and behaviours). A 1 standard deviation (SD) increase in SES was associated with a 0.12 decrease in EC ($p=0.05$), whereas poorer relationship quality was linked to a 0.18 increase in EC ($p=0.04$). Additionally, poorer sleep quality was linked with higher total CBCL scores ($\beta=0.15$, $p=0.01$) and increased externalizing symptoms ($\beta=0.10$, $p=0.056$). No other significant associations were observed.

Conclusion: These findings underscore the crucial role of prenatal factors, particularly socioeconomic status and relationship quality, in shaping children's emotional regulation, while maternal sleep quality is associated with externalizing problems. This highlights the need for a deeper understanding of the complex interplay of prenatal factors and their integration into interventions to enhance child developmental outcomes.

10 - Large Language Models for Electronic Health Records in Pediatric and Surgical Care: A Systematic Review

Carmel Daskalo[1, 2], Waseem Abu-Ashour[2], Jean Marie Tshimula[3, 4], Mohsen Amoei[1], Elena Guadagno[2], Dan Poenaru[1, 2]

[1]Faculty of Medicine and Health Sciences, McGill University, Montréal, Quebec, Canada, [2]Harvey E. Beardmore Division of Pediatric Surgery, The Montreal Children's Hospital, McGill University Health Centre, Montréal, Quebec, Canada, [3]Université de Sherbrooke, Sherbrooke, Quebec, Canada, [4]University of Kinshasa, Kinshasa, Democratic Republic of the Congo

Background: Large language models (LLMs) are increasingly seen as useful tools in healthcare, particularly for electronic health records (EHRs). Studies on the application of LLMs in pediatrics and in surgery are limited. Here, we evaluate the applications of LLMs in the EHR in pediatric and surgical care, their performance compared to traditional approaches, and their potential to improve healthcare processes, patient outcomes, and quality of care.

Methods: A senior medical librarian searched ten databases from inception until November 19, 2024. Studies were included if they used EHR datasets in pediatric or surgical domains, employed transformer-based LLMs, provided benchmark comparisons or relevant performance metrics, and were primary research articles. Two reviewers independently screened abstracts and full texts for inclusion. Data extraction is ongoing, and analyses will include descriptive and summative statistics.

Results: 4,344 studies were identified, of which 42 met the inclusion criteria. Among these, 29 (69.0%) focused on surgery, 3 (7.1%) on pediatric surgery, and 10 (23.8%) on pediatric care, covering a variety of subspecialties. The included studies span from 2021 to 2024, with the majority (61.9%) published in 2024 or later. LLMs were divided between BERT and its variants (22 studies, 52.4%), ChatGPT (13 studies, 31.0%), and others (7 studies, 16.7%). Most studies (81.0%) relied solely on retrospective, unstructured EHR data, of which half primarily focused on classification tasks. LLMs generally demonstrated improved performance in EHR-related tasks compared to traditional methods. Reported clinical translational applications included clinical decision support, diagnostic assistance, workflow optimization, and patient-physician communication.

Conclusions: This review provides preliminary insights into the role of LLMs in EHRs within pediatric and surgical settings. Further analysis will provide more detailed information on their applications, technical performance, and clinical potential, as well as their limitations and ethical considerations in these domains.

PhD – Senior

11 - Histone H3-K27M mutation drives AML by modulating gene expression

Bahareh Jafari[1, 2], Hassan Dakik[1, 3], Meaghan Boileau[4], Kolja Eppert[1, 3]

[1]Research Institute of the McGill University Health Centre, Montreal, QC, CANADA, [2]Division of Experimental Medicine, McGill University, Montreal, QC, CANADA, [3]Department of Pediatrics, McGill University, Montreal, QC, CANADA, [4]Department of Pediatric Oncology, Dana-Farber Cancer Institute, Boston Children's Hospital and Harvard Medical School, Boston, MA, USA

Single-cell RNA sequencing (scRNA-seq) from a human model of hematopoietic stem and progenitor cells (HSPCs) with the histone H3-K27M mutation has uncovered the involvement of genes in the development of acute myeloid leukemia (AML). AML is a highly aggressive and genetically complex hematological malignancy. Despite advances in its understanding, many aspects of AML progression remain elusive. Epigenetic mutations, particularly in histone H3, are critical early events in pre-leukemic HSCs, disrupting the balance of epigenetic marks and triggering leukemic transformation. Our previous research demonstrated that the H3-K27M mutation promotes the expansion of pre-leukemic HSCs by enhancing their frequency and self-renewal. In this study, we investigated the molecular mechanisms underlying H3-K27M-driven AML. scRNA-seq identified IGF2BP1 as one of the upregulated genes in H3-K27M versus wild-type HSCs. In vitro assays showed that IGF2BP1 inhibition partially rescues the phenotypes caused by the mutation in lineage-committed progenitors, particularly common myeloid progenitors (CMPs), without affecting wild-type cells. However, IGF2BP1 inhibition did not reverse the erythroid differentiation block induced by H3-K27M, suggesting an independent blockage mechanism. Future experiments will focus on earlier stages of erythroid differentiation and the effects of IGF2BP1 knockout via CRISPR. This research not only elucidates the role of histone H3-K27M in early AML but also highlights potential diagnostic, prognostic, and therapeutic targets for AML, advancing personalized treatment strategies.

PhD – Senior

12 - Are characteristics of neighbourhood environments associated with improvements in lifestyle behaviours among youth enrolled in the CANadian Pediatric Weight management Registry (CANPWR)?

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Introduction: It is unclear whether neighbourhood features can support the adoption of healthy lifestyles among youth followed in multidisciplinary obesity management clinics. This study examines associations between residential neighbourhood characteristics and changes in lifestyle behaviours (i.e., physical activity (PA), screen time and sleep duration) 1 year after initiation of obesity management care.

Methods: A secondary analysis of baseline and 1 year follow-up data of the CANadian Pediatric Weight management Registry (CANPWR) was conducted (n=481, 5-17 years). At both time points, questionnaire-assessed lifestyle behaviours included total PA, organized PA outside school, screen time, and sleep duration. Total and organized PA were operationalised as consistently unfavorable or worsening vs. consistently favorable or improving, and screen and sleep duration as consistently or newly not meeting vs. consistently or no longer meeting recommendations. Neighbourhood characteristics (walkability, greenness, material and social deprivation) were obtained for residential postal codes. Generalized Estimating Equations (GEE) were used examined associations between neighborhood characteristics and lifestyle behaviours. All models were adjusted for potential confounders (i.e., age at follow-up, sex, ethnicity, family income, and family structure).

Results: Participants residing in low (vs. high) material deprivation neighbourhoods were more likely to report consistently high or increased organized PA over 1 year (OR=2.62, 95% CI: 1.40-4.90). Participants living in greener neighbourhoods were less likely to always or newly meet screen time recommendations at 1 year (OR=0.49, 95% CI: 0.29- 0.84). Participants living in medium (vs. low) walkability neighbourhoods were more like to always or newly meet sleep duration recommendations at 1 year (OR=1.50, 95% CI: 1.05- 2.14).

Discussion: Residing in neighborhoods characterized with lower material deprivation, higher walkability was associated with maintenance or improvement of some health behaviours following 1-year of multidisciplinary obesity management care. Understanding how neighbourhood characteristics relate to the adoption of healthy lifestyle behaviours can guide the development of obesity management interventions that are tailored to the specific neighborhood environments.

Employee

13 - The Center for Applied Nanomedicine (CAN) - Integration of Analytical Technologies for Advanced Extracellular Vesicle and Particle Research

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[1]RIMUHC, [2]UdeM, [3]Soonchunhyang University, College of Medicine

The ever-expanding field of extracellular vesicle (EV) and particle (EP) research continually challenges conventional research instrumentation along the path to unravel their heterogeneous and intricate nature. In response, the Center for Applied Nanomedicine (CAN) at the Research Institute of the McGill University Health Centre (RI-MUHC) in Montreal, Canada, was pioneered as an integrated EV-dedicated research hub.

Supported by the Canada Foundation for Innovation (CFI), CAN harbors a broad arsenal of cutting-edge instrumentation. From nanoparticle tracking analysis (NTA; NanoSight & ZetaView) and microfluidic resistive pulse sensing (MRPS; nCS1) to nano-flow cytometry (nFC; CytoFLEX), imaging flow cytometry (iFC; ImageStream), chip-based fluorescent imaging (ChipFI; ExoView), nano-fluorescent sorting (nFS; CytoFLEX SRT), and super-resolution microscopy (NanoImager), CAN offers a comprehensive pipeline for EV and EP research. This research hub covers all stages of EV/EP analysis, from isolation and purification, followed by general characterization, to downstream applications, enabling researchers to delve deep into the complexity of EV/EP landscapes in health and disease. CAN interfaces with various facilities and new generation EV/EP analysis platforms, such as Raman spectroscopy as well as wet lab networks with bioassay capabilities.

CAN design has demonstrated an appreciable versatility and seamless integration within other core platforms at the RI-MUHC and within the multi-institutional McGill University network. Our experience suggests that a relatively humble investment, a central EV/EP lab may be established and poisitioned to play a pivotal role in enhancing research rigor, reproducibility, and promoting adherence to guidelines. Furthermore, such research hubs are vital in fostering interdisciplinary collaborations, uniting collective expertise, and promoting shared EV/EP research projects, thereby driving innovation and progress in the field.

Employee

14 - Formative Research to Inform the Design of a Multicomponent Parenting and Mental Health Promotion Intervention to Improve Early Child Development and Parent Outcomes

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Background: Multi-component parenting and parental mental health interventions have the potential to improve child and family well-being. However, most interventions do not adequately address parental mental health, and few of them engage in formative research to understand local contexts and ensure that interventions are addressing family needs. The objective of this study was therefore to explore local experiences of parenting and parental mental health to inform the development of a multi-component intervention for Ghanaian parents.

Methods: This study consisted of qualitative in-depth interviews and focus group discussions conducted in the Greater Accra region in southern Ghana in August-September 2024. The sample consisted of 83 adults including fathers, mothers, and other caregivers (e.g., grandparents) of children aged 6-60 months and respected community members (e.g., religious leaders and health workers). Data are being analyzed using thematic content analysis, and as of now 28 transcripts have been analyzed.

Results: Participants highlighted facilitators and barriers to their use of positive parenting practices and ability to support their mental health. Engaging in learning activities with children, maintaining a positive couple's relationship, financial stability, and participation in religious and social gatherings facilitated positive parenting. Barriers included financial difficulties, limited time with children due to work, and lack of paternal involvement. Supporting parental mental health was facilitated by religious engagement, financial stability, and strong social support, whereas financial difficulties, social isolation, and lack of access to mental health services were primary barriers. All parents and other caregivers expressed interest in attending a parenting and mental health support program, highlighting the need for accessible support.

Conclusion: Preliminary findings indicate that socioeconomic and social factors play a critical role in parents' abilities to engage in positive parenting practices and care for their mental health. Further analysis will deepen these insights and inform the development of a contextually-relevant intervention.

Undergraduate student - Junior

15 - Acculturation in Young Latino Immigrants and its Perceived Impact on their Mental Health

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Background: Acculturation is the process of cultural change in which individuals adopt, resist, or modify the values, beliefs, and behaviors of their heritage and host cultures. Among Latino immigrants, acculturation has been linked to various mental health outcomes, yet research has largely relied on quantitative approaches thus precluding a nuanced understanding of acculturation. Furthermore, there is limited understanding of how Latino immigrants experience acculturation in Canada and how it may influence their mental health. This study qualitatively examined the experience of acculturation in young Latino immigrants living in Canada.

Methods: In-depth interviews of around 30 minutes were conducted in Spanish or English, in person or online, with eight Latino immigrants (ages 18-25). The language and modality of the interview were the participant's preference. A semi-structured topic guide including questions on the affective, cognitive, and behavioral components of acculturation, and their emotional effects was used. Convenient and snowball sampling techniques were used. Data analysis using thematic content analysis is ongoing.

Results: Participants were first-generation immigrants, arriving in Canada between ages 7 and 15. Acculturation was marked by both negative and positive feelings, with participants expressing simultaneous attachment to and gratitude for both cultures yet feeling that they did not belong to one or the other. Key heritage values included family, respect, community, and faith, which shaped decision-making in different ways over time. Host culture values—multiculturalism, respect, and independence—helped participants navigate society. Social relationships were perceived as warmer in heritage but colder in host cultures, contributing to feelings of exclusion. Language played a crucial role in confidence and mental well-being.

Conclusion: Acculturation is a complex, evolving process with important mental health implications. Further analysis will deepen understanding of how its cognitive, affective, and behavioral dimensions shape young Latino immigrants' well-being in Canada.

16 - Pediatric core outcome set in a group of rare musculoskeletal diseases: Protocol for co-development with international stakeholders and initial findings

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COMET Registration: https://www.comet-initiative.org/Studies/Details/3378

Introduction: Ongoing research for Arthrogryposis multiplex congenita (AMC), advocates for holistic and family-centred interventions. However, clinicians working with children with AMC are often met with gaps in the literature and a lack of guidelines, impacting services. Current limitations in clinical practice demonstrate the need for consensus on which outcome measures to use in pediatric rehabilitation for AMC.

Objectives: To develop a core outcome set (COS) for a group of rare musculoskeletal diseases (AMC), fostering standardized and inclusive care practices.

Methods: The study follows a mixed-method multiphasic approach, adhering to the COMET Initiative's standards for development (COS-STAD).

To begin, an advisory panel was formed, representing clinicians and individuals with lived experience from Canada, USA, Poland, Australia and India. Rehabilitation needs and preliminary measures were then identified through a global survey/ scoping review, common data elements, and the 2025 Consensus-Based Rehabilitation Recommendations for AMC. In phase 1, the panel was asked to evaluate preliminary concepts, complete an initial appraisal of the selected outcome measures, and recommend additional measures if needed. Responses were then analyzed in preparation for phases 2-5. Upcoming phases include (2) ICF mapping of selected measures via Cosmin Guidelines; (3) COS selection; (4) expert meetings, modified Delphi rounds and international focus groups; (5) external methodological appraisal. **Practice Implications:** The development of a COS can facilitate the choice of relevant and valid measures for children with AMC. Projected practice implications may include the streamlining of rehabilitation services, improved collaboration between practitioners and optimized quality of care worldwide.

PhD – Senior

17 - DECODING MALE FERTILITY: PROTEIN COALATION AS A NEGATIVE BIOMARKER

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Male infertility is rising, but semen analysis methods have seen little progress in over 50 years. With no reliable biomarker of sperm function, conventional semen analysis fails to diagnose 30% of infertility cases, classifying them as unexplained male infertility. Capacitation, a prerequisite process required for sperm function, requires controlled oxidation and redox signaling. CoAlation, is a novel redox modification mediated by Coenzyme A (CoASH), protecting proteins from oxidation and regulates their redox signaling. We previously reported a dynamic decrease in CoAlation levels before capacitation and hypothesize that CoAlation regulates redox activation of proteins essential for capacitation. Our objectives were to : (1) investigate CoASH biosynthesis and its regulation of CoAlation in human sperm and (2) examine the role of CoAlation on redox-dependent processes during capacitation.

Fetal cord serum ultrafiltrate (FCSu) was used to induce capacitation in human spermatozoa with or without CoASH biosynthetic modulators. Levels of CoAlation was assessed by immunoblotting and capacitation was assessed by phosphorylation of PKA substrates (pPKAS), tyrosine phosphorylation (pTYR) (immunoblotting), and acrosome reaction (PSA-FITC microscopy).

We demonstrated that human spermatozoa possess the enzymatic machinery for de novo CoASH biosynthesis and undergo dynamic CoAlation during capacitation. Protein CoAlation negatively influences redox-dependent processes during capacitation. The oxidation-induced dimerization of 45kDa PKA-R identifies a potential protein target of CoAlation in redox signaling during sperm capacitation. Protein CoAlation serves as a protective mechanism, shielding PKA-R thiol groups from premature oxidation and dimerization, suggesting a new role of CoASH as a decapacitation factor. The observed deCoAlation during capacitation may be necessary to expose these thiols at the appropriate time, facilitating redox-dependent oxidation and dimerization of PKA-R. These findings highlight protein CoAlation as a negative biomarker of human sperm capacitation and suggest its potential as a parameter for assessing sperm function in male fertility evaluations.

Supported by a CIHR.

PhD – Senior

18 - Prenatal Risk Factors in Septo-Optic Dysplasia

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Introduction/Aim: Midline brain malformations encompass a spectrum of congenital anomalies affecting structures along the midline of the brain, including the corpus callosum, pituitary gland, and optic nerves. These malformations can lead to significant neurological deficits and developmental delays. The etiology of midline brain malformations is complex and multifactorial, involving both genetic and environmental factors. This study examines patients with septo-optic dysplasia (SOD), a rare congenital condition characterized by underdevelopment of the optic nerves and pituitary gland. Understanding the risk factors associated with these malformations is crucial for early detection, intervention, and adequate follow-up.

Materials/Methods: A retrospective cohort study of children with SOD was conducted using medical records from the McGill University Health Centre and Genova University, Italy over a ten-year period. Patients fullfilling the criteria for septo-optic dysplasia were included. Demographic data, family history, maternal health records, and genetic testing results were analyzed. **Results:** This multi-center study examined 51 participants with SOD (26 male, 25 female; average age 12.4 years). Seventy-five percent of the cohort was classified as having “SOD plus”, ie brain imaging demonstrated additional anomalies. Prenatal risk factors were frequently reported and included young maternal age (<20 years) in 17% and substance usage during pregnancy in 24%. Neonatal complications were observed in 80% of the cohort. The diagnostic yield of genetic testing was low (<4%), further supporting the hypothesis that non-genetic, potentially acquired factors—such as biological and environmental influences—may play a predominant role in the etiology of SOD.

Significance: This research offers a thorough exploration of SOD, highlighting the importance of systematically identifying risk factors in patients with septo-optic dysplasia to enhance both understanding and clinical management of these complex congenital anomalies.

Employee

19 - Bilateral Cortical Activity in Congenital Mirror Movement Syndromes.

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Congenital Mirror Movement (CMM) is a rare syndrome where any voluntary movement of a limb is simultaneously accompanied by an unvoluntary, mirrored movement of the opposite limb. The involuntary movements mostly affect the upper extremity of the body, particularly the hands and fingers. This condition therefore causes considerable manual dexterity impairments. While CMM is caused by mutations in multiple genes, genotype-phenotype associations have yet to be fully determined. One major hypothesis suggests that CMM results from abnormal bilateral corticospinal tract projections, where each motor cortex has both a normal crossed projection to the opposite limb and an abnormal uncrossed projection to the same-side limb. However, other hypotheses suggest a cortical cause. We conduct the first neurophysiological characterization of CMM using magnetoencephalographic imaging (MEG) to identify dynamics of atypical bilateral cortical activity during unilateral motor tasks and tactile stimulation in CMM patient participants. Our pilot results confirm that bilateral motor and premotor cortical activity occurs with finger movements, whereas tactile stimulation evokes typical contralateral activation. This demonstrates that involuntary movements of the ipsilateral limb involve the contralateral pre/motor cortex, suggesting that mirror movements are not solely due to abnormal uncrossed corticospinal projections. Time-resolve imaging refines our understanding of the brain dynamics underlying a disorder with clear behavioral elements such as CMM, advancing a broader comprehension of motor control.

Employee

20 - The role of TMED2 in craniofacial development

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[1]RI-MUHC, [2]McGill

TMED2 is a member of the transmembrane emp24 domain protein family required for cargo transport between the ER and Golgi. We identified a mutant mouse line with a loss of function point mutation in the Tmed2 signal sequence ($Tmed2^{99J}$) in a screen for genes required for proper morphogenesis. We found that $Tmed2^{99J}$ homozygous mutant embryos die at E11.5 due to placental defects. These mutants display developmental delay, failure to turn, posterior truncations, abnormal heart looping, and abnormal head development. Recently, we generated mutant mouse lines with LoxP sequences flanking exons 2 and 3 of Tmed2 to investigate its tissue-specific requirements during embryogenesis. Using beta-actin Cre, we generated mice with heterozygous deletion of Tmed2 and confirmed that the two mutant alleles failed to complement. While Tmed2 heterozygous mice ($Tmed2^{+/-}$) resembled controls, Tmed2 homozygous mice ($Tmed2^{-/-}$) arrested at E8.5 and showed developmental delay with a significant decrease in mRNA levels. Deletion of Tmed2 in neural crest cells using Wnt1-Cre resulted in abnormal cranial nerves formation at E10.5. Cartilage and skeletal preparation of E14.5 and E18.5 neural crest mutant embryos showed microcephaly and micrognathia, as well as reduced frontonasal cartilage and poor ossification in the mandible and bones of the head derived from neural crest cells. Using the mTmG reporter, we further observed that there was a loss of neural crest-derived cells at E18.5. These results indicate that TMED2 is required in the neural crest cells for normal development of the head. Future studies will focus on identifying the TMED2 cargoes important for craniofacial development.

Undergraduate student - Junior

21 - Racial and ethnic disparities in timing of diagnosis of neurodevelopmental disorders: A Systematic Review

Emily Pun[1], Ugochinyere Ukah[1]

[1]McGill University

Racial and ethnic disparities in timing of diagnosis of neurodevelopmental disorders: A Systematic Review

ABSTRACT

Background: Delay in diagnosis of neurodevelopmental disorders (NDDs) is linked with worse health outcomes and poorer quality of life for patients. Racial and ethnic disparities have been reported in NDD prevalence but less is known about racial disparities in timing of NDD diagnoses, except for autism spectrum disorder (ASD).

Objective: To systematically review and synthesize studies reporting associations between race and ethnicity with age of NDD diagnosis.

Method: We searched Medline, EMBASE, CINAHL, and PsycInfo from inception to December 2024 for studies comparing the age of NDD diagnosis by racial and ethnic groups. We included all types of NDD e.g., Attention-Deficit/Hyperactivity Disorder (ADHD) and epilepsy, except those reporting only on ASD. We narratively summarised findings from eligible studies.

Results: Of 6098 publications initially screened, 11 studies were eligible for inclusion. Included studies examined various NDDs, including epilepsy (N=4), ADHD with or without ASD (N=4), developmental delay (N=2), and Tourette syndrome (N=1). These studies spanned across 4 countries (Canada, USA, Israel, and Australia). There was heterogeneity in reported findings although more studies reported a greater delay in diagnoses for Black, Indigenous, and People of Color (BIPOC) groups compared with White patients.

Conclusion: Racial and ethnic disparities may exist in timing of NDD diagnoses. Addressing factors associated with delayed NDD diagnoses is important to support future interventions and early initiation of treatment to improve outcomes for patients.

22 - Elucidating the extracellular vesicle signature of K27M oncohistone-driven pediatric high-grade gliomas

Samia Jahouri[1], Laura Montermini[1], Nadim Tawil[1], Mahsa Jalali[1], Wajih Jawhar[1], Brian Meehan[1], Dan Ghiran[1], Fereshteh Shojaeighahrizjani[1], Damien Faury[1], Nada Jabado[1], Janusz Rak[1]

[1]RI-MUHC

Diffuse midline gliomas (DMGs) are aggressive pediatric brain tumours with a poor prognosis. About 80% of DMGs carry the oncogenic H3K27M histone H3 mutation, disrupting histone modifications and stalling differentiation in glial cells. The absence of biomarkers precludes non-invasive diagnosis and precision monitoring of standard and experimental therapy in DMG. These oncogenic mutations impact the representation of cancer-related material in extracellular space and biofluids, including the content of extracellular vesicles (EVs). This represents a new dimension in liquid biopsy diagnostics, a non-invasive strategy predicated on the detection of cancer-associated biomarkers in bodily fluids. EVs are nano-sized particles, secreted by tumour cells, that carry a multiplexed repertoire of tumour-specific DNA, RNA, and protein cargo reflecting tumour biology, heterogeneity and progression.

This study seeks to define diagnostically useful properties of DMG EVs which would be reflective of epigenetic and biological alterations driven by the H3K27M oncoprotein to develop new liquid biopsy approaches for monitoring DMG progression and treatment. We characterized the EV profiles of DMG cells with and without the K27M mutation and explored the feasibility of detecting the mutant oncoprotein in EVs both in vitro and in vivo. Nanoparticle tracking analysis (NTA) revealed a heterogeneous population and vesicles with a size range typical of small EVs. Western blot analysis confirmed canonical EV markers (e.g., CD9, CD63, TS101) and stemness-associated proteins (CD133), enriched in H3K27M-mutant cancer stem cells and EVs. ExoView analysis documented the heterogeneity of EV subpopulations released from DMG cells. Most importantly, our results revealed that H3K27M mutant histones are retained within EVs, reflecting the epigenetic state of the parental tumour cells.

These findings could pave the way for novel non-invasive liquid biopsy diagnostics and real-time monitoring of DMGs using EVs carrying the key oncogenic driver, an important step in advancing personalized care for children with this intractable disease.

PhD – Senior

23 - Identification of novel genes and variants underlying human reproductive failure

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Reproductive failure including infertility, recurrent miscarriage (RM), and recurrent hydatidiform mole (RHM) affects millions of individuals globally and remains largely unexplained in the majority of cases. To uncover novel genetic causes of reproductive failure, we conducted whole-exome sequencing on 27 unrelated patients/couples including five familial cases, prioritizing rare homozygous or compound heterozygous variants consistent with a recessive mode of inheritance.

Our analyses revealed pathogenic or likely pathogenic variants in several patients. These include (1) a novel homozygous variant in RNF212B causing exon skipping and likely disrupting crossover formation, affecting fertility; (2) TUBB8, known to be critical for spindle function in meiosis. (3) In a female patient with five miscarriages, failed ICSI, and a 14-year history of infertility, we identified a homozygous CCDC39 variant. This is the most plausible cause of her infertility, supported by segregation in affected siblings and CCDC39's known role in primary ciliary dyskinesia and reproductive failure. (4) a homozygous AGBL5 variant in a male with oligoospermia, retinitis pigmentosa, and cataract. While mouse studies link AGBL5 to spermatogenesis via tubulin deglutamylation, our case provides the first evidence of its role in human male infertility. (5) A homozygous variant in PLCZ1 was identified in a male partner of an infertile couple; this gene is known to impair oocyte activation and may explain a first-trimester loss. (6) We also identified a deleterious variant in FBXO43, a gene important for meiotic progression. Functional studies such as minigene assays validated the impact of select variants on gene function. In parallel, we are using C. elegans to model the RNF212B mutation and assess its effect on female fertility.

This integrative approach revealed causative variants in ~25% of analyzed cases, highlighting the value of combining genetic testing with clinical data and functional validation in reproductive genetics. Our findings expand the mutational landscape of reproductive failure and offer insights that may inform counseling and potential therapeutic strategies.

PhD – Senior

24 - Modeling Axial Skeletal Abnormalities in Cerebro-Costo-Mandibular Syndrome (CCMS) with Tamoxifen-Induced Snrpb Deletion

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Cerebro-Costo-Mandibular Syndrome (CCMS) is a rare congenital disorder caused by heterozygous mutations in SNRPB, a core component of the spliceosome, and is characterized by craniofacial malformations and rib abnormalities. To investigate the molecular mechanisms underlying CCMS, we generated a tamoxifen-inducible murine model with ubiquitous heterozygous deletion of Snrpb. Tamoxifen-induced Snrpb deletion at embryonic day (E) 8.5 allowed us to bypass early embryonic lethality and recapitulate key CCMS abnormalities, including posterior rib gaps, a bell-shaped thorax, and craniofacial defects in late-stage embryos. This model serves as a valuable tool for studying the pathogenesis of CCMS.

To identify molecular changes contributing to rib and vertebral abnormalities, we performed bulk RNA sequencing of somite tissues from E9.5 control and mutant embryos. Somites are transit structures of the paraxial mesoderm that develop into the dermomyotome and sclerotome; the sclerotome later forms the vertebrae, intervertebral discs, and ribs. In mutants, retinoic acid (RA) signaling, essential for axial skeletal development, was disrupted. Specifically, impaired RA synthesis and increased degradation likely led to reduced RA activity, disrupting the expression of downstream target genes that regulate somite differentiation and contribute to sclerotome development.

To further assess RA activity in vivo, we plan to incorporate a reporter mouse line, which expresses β-galactosidase under the control of an RA response element, allowing us to visualize and quantify RA signaling levels during embryonic development. Additionally, we will investigate whether dietary RA supplementation can rescue axial skeletal abnormalities, offering insights into potential therapeutic strategies for CCMS.

Employee

25 - Arsenic exposure impairs podocyte development in human kidney organoids

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Arsenic is a widespread environmental contaminant, with millions of Canadians potentially exposed to levels above Health Canada's 10 ppb limit. While adult exposure increases kidney disease risk, its impact on kidney development is unknown. In this study, we performed an arsenic toxicity screen during nephron development using induced pluripotent stem cell (iPSC)-derived human kidney organoids.

Using an innovative suspension culture method, we generated ~5,000 human kidney organoids per well, each with ~10 nephron-like tubules. Arsenic exposure began at the iPSC stage and continued through differentiation to intermediate mesoderm and mature kidney organoids, simulating exposure from conception to the end of nephrogenesis. Low-dose arsenic concentrations were used (0, 25 and 50 ppb), mimicking real-life exposures in Canada.

Kidney organoids exposed to 0 and 25 ppb of arsenic during nephrogenesis had normal tubule development, with expression and localisation of nephron markers PODXL and WT1 (podocytes), LTL (proximal tubules) and E-cadherin (distal tubules). In contrast, kidney organoids exposed to 50 ppb had a marked reduction in WT1 and PODXL-positive cells, but an increase in LTL and E-cadherin-positive cells, suggesting arsenic affects cell fate decisions and nephron differentiation. We also developed a deep-learning tool to extract unbiased morphological features from thousands of brightfield images, and principal component analyses showed that 50 ppb kidney organoids follow a distinct developmental trajectory.

Our study identified that the developing kidney is vulnerable to low levels of arsenic toxicity, impairing the development of podocyte-like cells in human kidney organoids. This work yields insight into the developmental origins of arsenic-related kidney disease.

26 - Mechanism of Pre-Leukemic HSC Expansion Driven by H3-K27M Mutations

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The onset of acute myeloid leukemia (AML) is preceded by a pre-leukemic phase in which early mutations arise in hematopoietic stem cells and progenitors (HSPCs) causing clonal expansion of these mutated yet still functional cells. Some of these cells eventually acquire additional mutations to become leukemia stem cells (LSCs) which cause and sustain the disease. Pre-leukemic mutations often occur in “landscaping genes” such as epigenetic regulators resulting in global DNA organizational changes and aberrant expression of many genes. One such early mutation identified in leukemia is H3K27M; a lysine-to-methionine substitution at position 27 of the histone 3 tail. This mutation is known to increase proliferation and myeloid colony-forming potential of human HSPCs however, the genes acting downstream of H3K27M to cause these effects still need to be identified. The aim of this project is to determine the mechanism of how the H3K27M mutation expands pre-leukemic stem cells. Through comparison of RNA expression data from wildtype and mutant human CD34+ HSPCs, AML patient samples, and a hematopoietic cell line we have generated a list of candidate genes consistently overexpressed in mutant cells. Using CRISPR/Cas9 editing we will knockout candidate genes in both wild-type and H3K27M transduced cells while tracking proliferation and colony-forming potential to investigate whether the candidate genes are essential for the H3K37M phenotype. This project will identify the genes through which this histone mutation drives clonal expansion of pre-leukemic stem cells in order to further our knowledge of leukemogenesis and point to a vulnerability that can be leveraged against leukemia stem cells harbouring the H3K27M mutation.

27 - Associations of Diabetes Stigma and Diabetes Distress with Body Mass Index Among Adolescents with Type 1 Diabetes Before Transition to Adult Care

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Background: Adolescents with type 1 diabetes (T1D) face unique challenges in disease management, with diabetes-related stigma and distress contributing to suboptimal self-care and increased mental health burden. While stigma and distress are associated with glycemic outcomes, their relationship with body mass index (BMI) —a factor of well-being and indicator of glycemic control and cardiometabolic risk— is unknown.

Objectives: We examined associations of diabetes-related stigma and diabetes distress with BMI in adolescents with T1D in older adolescents and determined whether socioeconomic status (SES) or sex modified associations.

Methods: We conducted a cross-sectional analysis of baseline data of adolescents (ages 16-17) with T1D followed at 2 academic hospitals in Montreal, Canada, and enrolled in the Group Education Trial to Improve Transition in Adolescents with T1D. Participants completed validated questionnaires on perceived diabetes stigma (Barriers to Diabetes Adherence stigma subscale) and diabetes distress (Diabetes Distress Scale for Adults with T1D). Primary outcome was z-BMI scores. Associations of stigma and distress with z-BMI were assessed using multivariable linear regression, adjusted for SES, sex, technology use, mental health comorbidities, A1C, and diabetes duration. We examined interaction terms for SES and sex.

Results: Of 185 adolescents with T1D (100, 51.1% female; Mean±SD age:16.8±0.2 years; diabetes duration: 7.6±4.3 years; z-BMI: 0.82±0.80), 115 (62.2%) reported diabetes-related stigma and 38 (20.5%) reported diabetes distress. Adolescents with stigma compared with those without stigma had higher z-BMI (β = 0.31, 95% CI 0.01 to 0.61; p=0.045). We observed no evidence of association between diabetes distress and z-BMI or interactions with sex and SES.

Conclusions: Higher levels of diabetes-related stigma are associated with higher BMI in adolescents with T1D transitioning to adulthood and adult care. This association is maintained across sex and SES groups. Interventions targeting perceived diabetes-related stigma in adolescents may prevent overweight or potential cardiometabolic risk in T1D.

PhD – Senior

28 - Dysregulated sphingolipid and cholesterol levels promotes oxidative stress in human spermatozoa

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INTRODUCTION:

The impact of dyslipidemia on semen quality and male fertility is poorly understood. Lipid rafts are sphingolipid and sterol-rich organizing centers that affect membrane proteins, receptor activation, and signalling pathways. Sphingosine (Sph), Ceramide (Cer), Sph-1P, and Cer-1P are bioactive molecules that we have shown to promote capacitation-associated modifications, such as in nitric oxide ($NO^{\bullet}$) and superoxide ($O_2^{\bullet-}$) production, PI3K (P-PI3K) and tyrosine (P-Tyr) phosphorylations, and progesterone-induced acrosome reaction (Hum Reprod, 2025). A high-cholesterol or high-fat diet can lead to hypercholesterolemia/hyperlipidemia and negatively affect the functionality of human sperm. However, the specific molecular mechanisms are not well understood. We hypothesized that elevated Sph, Cer, and cholesterol will promote oxidative stress and oxidative damage through lipid peroxidation, DNA damage, loss of mitochondrial membrane potential (MMP), and tyrosine nitration of sperm proteins. Our objectives were: 1) To determine whether high doses of Sph and Cer and cholesterol impair capacitation-associated modifications, and 2) To determine if there is an increase in sperm damage resulting from elevated levels of sphingolipids and cholesterol.

METHODS:

Highly motile human spermatozoa were incubated in BWW medium for 4h at 37°C, with or without our capacitation inducer Fetal Cord Serum ultrafiltrate (FCSu), Sph or Cer, Cholesterol-sulfate (Chol-SO_4), methyl-b cyclodextrin (MβCD), and subjected to pharmacological inhibition of nitric oxide synthase (NOS), S1PR1, of $O_2^{\bullet-}$ production by superoxide dismutase, and neutral Sphingomyelinase (nSMase). P-Tyr and P-PI3K levels were determined by immunoblotting. Localization and cholesterol efflux studies were conducted through fluorescence microscopy using BODIPY-Cholesterol. Acrosome reaction (AR) and tyrosine nitration were assessed using PSA-FITC using fluorescence microscopy and immunoblotting, respectively. $NO^{\bullet}$ production (DAF2-DA), lipid peroxidation (BODIPY-C11), DNA damage (8-OHdG), mitochondrial $O_2^{\bullet-}$ production (MitoSOX), and mitochondrial membrane potential (JC-1) were assessed by flow cytometry. Sperm $O_2^{\bullet-}$ production was determined by chemiluminescence. Sperm motility and viability were evaluated using CASA system and HOS test, respectively.

RESULTS:

MβCD induced capacitation by promoting cholesterol efflux, increased P-PI3K and P-Tyr levels, ROS production, hyperactivation, and AR. Inhibition of nSMase impaired MβCD-induced cholesterol efflux and P-Tyr. Elevated Chol-SO_4, Sph and Cer impaired P-Tyr, motility and viability, and increased lipid peroxidation, DNA oxidation, MMP and tyrosine nitration.

CONCLUSIONS:

Elevated cholesterol, Cer, and Sph, impair capacitation by inducing oxidative stress-induced damage in spermatozoa. The findings suggest that disruptions in lipid metabolism, resulting from conditions like obesity, can interfere with fertilizing potential in men, providing new insights into male infertility mechanisms and emphasizing the need to monitor and manage the serum lipid profiles of infertile males.

Supported by CIHR grants (PJT-165962 and PJT-191704 to CO) and RI-MUHC Desjardins Studentship to SS.

Post-doc - Senior

29 - Assessing extracellular vesicles as biological indicators for placental complications in the mouse

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The placenta regulates fetal-maternal communication, ensuring proper fetal growth and development. Impaired placental function contributes to pregnancy complications such as preeclampsia and intrauterine growth restriction (IUGR). However, early diagnosis remains challenging due to the invasive nature of placental sampling. Extracellular vesicles (EVs), which facilitate intercellular communication and reflect placental function, have emerged as promising non-invasive biomarkers. This study investigated whether placental EVs could detect pregnancy complications early using a Nodal knockout mouse model.

Mid-gestational phenotypes were characterized, and placental EV cargo was analyzed for molecular markers of dysfunction. Placental extracellular vesicles were isolated from D10.5 placenta using enzymatic digestion, differential centrifugation, filtration, and size-exclusion chromatography. Characterization included size analysis, classical protein marker abundance, and morphology assessment to confirm EV purity and integrity.

Uterine-specific deletion of Nodal resulted in increased IUGR and fetal loss, with significantly fewer viable implantation sites and embryos that were either smaller or resorbed during mid-pregnancy. Defects in decidualization and placentation were observed, including thinner decidual and placental tissues, as well as impaired angiogenesis marked by reduced Cd31 expression. Increased parietal trophoblast giant cells suggested differentiation defects or a compensatory response to poor vascularization. Proteomic and miRNA-Seq analysis of EV cargo identified 30 differentially expressed proteins and 13 miRNAs linked to placental development, oxidative stress, angiogenesis, and immune modulation. Notably, 9 proteins and 4 miRNAs had been previously associated with pregnancy complications. Functional enrichment analysis highlighted disruptions in vascular function, hormone signaling, and inflammation, further supporting the role of placental EVs as biomarkers for pregnancy complications.

These findings suggest that placental EVs reflect placental dysfunction and could serve as non-invasive biomarkers for early detection of pregnancy complications. Their diagnostic utility may improve maternal and neonatal health outcomes by enabling earlier intervention and monitoring of at-risk pregnancies.

30 - The Role of TMED2 on Murine Cardiac Development

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The transmembrane emp24 domain (TMED) proteins are essential components of the secretory pathway, mediating protein transport via coat protein (COP)-coated vesicles. TMED proteins act as cargo receptors, regulating selective protein trafficking between the endoplasmic reticulum (ER) and the Golgi apparatus. Disruptions in this transport pathway can impair cell differentiation and fate determination, leading to congenital malformations. TMED2, a member of the TMED β subfamily, is particularly critical for normal embryonic development in mice. Previous studies have demonstrated that a single-point mutation in Tmed2 ($Tmed2^{99J/99J}$) results in embryonic lethality by mid-gestation, with early-stage embryos exhibiting abnormal development, including randomized heart looping. These findings suggest a key role for TMED2 in cardiac morphogenesis, though the underlying molecular mechanisms remain unclear. We hypothesize that disrupted protein transport between the ER and the Golgi in Tmed2 mutants disrupts cardiac development, leading to abnormal heart morphogenesis. To investigate this, we employ a conditional mutant mouse model with LoxP sequences flanking exons 2 and 3 of Tmed2. Using Mesp1-cre, which is expressed in mesodermal cells contributing to the developing head and heart, we mutated Tmed2. Additionally, we conditionally mutated Tmed2 in neural crest cells using Wnt1-cre, as cardiac neural crest cells contribute to outflow tract elongation and septation as of E10.5, forming the pulmonary trunk and aorta. Preliminary histological analysis at E11.5 has showed that $Tmed2^{LoxP/LoxP}$; $Mesp1\text{-}cre^{+/-}$ embryos display normal heart looping but may exhibit defects in endocardial cushion development. Furthermore, at E11.5 $Tmed2^{LoxP/LoxP}$; $Wnt1\text{-}cre^{tg/+}$ embryos show normal neural crest cell migration but fail to septate the outflow tract into two distinct vessels needed to separate the systemic and pulmonary circulation, suggesting a critical role for TMED2 in this process.

Employee

31 - Dental and craniofacial features in arthrogryposis: Imaging, oral health-related quality of life and phenotype

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Background: Multiple congenital contractures are the most salient clinical feature of arthrogryposis multiplex congenita (AMC). Contractures can affect all joints, including the jaw, and therefore may affect oral health. The findings of a scoping review we conducted showed that there is lack of evidence concerning dental and maxillofacial manifestations in AMC. This underscores the need for interdisciplinary collaboration and the undertaking of extensive prospective cohort studies focused on AMC. **Objectives:** To define the dental and craniofacial phenotype using clinical examinations and imaging and describe the oral health-related quality of life (OHRQoL) of children with AMC using patient-reported outcomes. **Methods:** We will recruit 15 children between 3 and 25 years of age with AMC at Shriners Hospital for Children in Montreal, Canada. Upon obtaining written consent, the first visit will entail having the parent of the child (3-25 years) complete the Child Oral Health Impact Profile (COHIP) preschool or short form Proxy version, Pediatric Sleep Questionnaire, and a clinical information form at the Shriners Hospital. The child 7-25 years of age will complete the COHIP questionnaire and undergo extra- and intra-oral photographs as well as a clinical examination. A second visit, at the McGill dental clinic will then be scheduled to complete a Panorex and/or Cone Beam CT based on the child's age and capacity. Imaging will be analyzed by a pediatric dentist and an oral and maxillofacial radiologist. Descriptive statistics will be used to analyze continuous variables (e.g., age, number of missing or impacted teeth, overjet, overbite, mouth opening), categorical data will be calculated in numbers and percentages (e.g., presence/absence of cleft palate, micrognathia, gingivitis, periodontitis). OHRQoL scores will be presented as means and compared to normative data. **Expected contribution:** Our results will help us better understand the variations in dental and maxillofacial features in AMC to help guide and promote better oral care and health in this group of rare conditions.

PhD – Senior

32 - THE REQUIREMENT OF SNRPB IN MESODERM FOR THE DEVELOPMENT OF THE AXIAL SKELETON

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The axial skeleton develops from mesoderm and neural crest cells. Recent research aims to uncover the role of splicing in this process. Mutations in splicing factors lead to spliceosomopathies such as **C**erebro**c**osto**m**andibular **S**yndrome, which is characterized by axial defects. These defects lead to respiratory insufficiencies and in 50% of cases, death in neonates. Patients carry pathogenic variants in the splicing gene SNRPB. SNRPB is required in neural crest cells for craniofacial development, however, its role in mesoderm remains elusive. I **aim** to understand how Snrpb mutation in mouse mesoderm causes axial defects.

Using Mesp1-Cre and Snrpb conditional mutant mice, I deleted Snrpb in the anterior mesoderm, specifically the head and anterior somites. Alcian blue and alizarin red were used to analyze cartilage and bone formation. Whole-mount in situ hybridization and immunofluorescence were used to analyze the localization of genes and proteins important for axial development.

Mutants had microcephaly, micrognathia, small bell-shaped thorax and scoliosis. Preliminary data suggests that Pax1, a sclerotome determinant, was increased in the anterior somitic region. Fibronectin, integral throughout skeletal development, was mislocalized and appeared reduced in mutants. Future experiments will assess other associated axial genes and use Brachyury(T)-Cre to induce Snrpb deletion in posterior mesoderm. Genes that are alternatively spliced in mutants will be identified, and their roles in axial development assessed.

These findings confirm Snrpb's mesodermal role in axial development and its upstream regulation of key axial factors. This research is significant as it aims to understand causative pathways of potentially fatal defects to reduce neonatal mortality.

Funding Sources: Supported by the Canadian Institute of Health Research; Research Institute at McGill University Health Center - Desjardins Studentship in Child Health Research; Lloyd-Carr Harris Fellowship; Department of Anatomy and Cell Biology, McGill University

33 - Parental Mental Health in Africa: A Brief Literature Review

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Introduction : Parental mental health plays a vital role in family wellbeing. Despite the higher burden of depression in parents living in Africa, their mental health problems remain under-recognized and undertreated. There is also little research on the positive dimensions of parental mental health, as well as the mental health of fathers. To inform future research on parental mental health in Africa, we ought to summarize existing evidence on maternal and paternal depression and positive mental health across the continent.

Method : A systematic search was conducted using PubMed and Scopus. Search terms included 'parental depression', 'parental mental health', and 'parental positive mental health' were used. Studies were included if they examined the mental health (depression and/or positive mental health) of parents living in Africa and were published between 2011 and 2024.

Results : The initial search yielded 328 articles, with 24 meeting inclusion criteria. These included longitudinal (n=4), cross-sectional (n=10), systematic reviews and meta-analyses (n=7), and mixed-method (n=3) studies. Twelve studies were conducted in Ghana and, one each in Ethiopia, Nigeria, and other countries. The prevalence of depression ranged from 19.7% to 50.5% in mothers and 8.8% to 20.8% in fathers. Key risk factors for maternal depression included lack of social support and single motherhood. For fathers, unemployment and substance use were predominant, while marital distress and unplanned pregnancy affected depression in both parents. Only 6 studies included a measure of positive mental health, identifying it as a key protective factor that enhanced recovery from mental illness and improved overall well-being.

Conclusion : There continues to be a dearth of research examining parental mental health, particularly paternal and positive mental health, in Africa. Further research is needed to understand the burden of mental health and shed light on how services and interventions can better support parents and families.

34 - Coupled AI-powered-in vitro drug discovery strategy targeting oncogenic fusion proteins driving AML

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Gene rearrangements play a key role in initiating acute myeloid leukemia (AML), leading to the generation of oncogenic fusion proteins. AML develops in a multistep process with mutations accumulating in normal hematopoietic stem cells until full leukemogenesis. The RUNX1-ETO and CBFβ-MYH11 fusion proteins are found in 25% of pediatric AML cases and these founding mutations represent ideal therapy targets. However, blocking them is challenging due to their molecular mechanisms and interaction with numerous co-factors, and are usually considered "undruggable". By developing novel AI-powered tools coupled with in vitro assays to identify molecules that can inhibit fusion protein function, we will accelerate the discovery of novel therapies. With AI-powered tools (protein modeling, docking, toxicity prediction), we identified small molecules predicted to interfere with the fusion proteins. Then, in vitro evaluation was done in cellular models to obtain LC50 values. More than 60 combinations of fusion protein cellular models and molecules have been tested to date. 7/19 of the molecules showed potency below 5 µM, making them candidates for advancing to a hit-to-lead phase. Furthermore, potential toxicity was assessed using CD34+ cord blood stem cells. Specificity evaluations are being conducted using the reporter protein CD34 regulated by the RUNX1-ETO fusion. The next steps include shRNA fusion protein knockdown to validate the on-target effect of the molecules. Our preliminary results obtained in 1 year confirm that novel AI-powered tools coupled with in vitro validating strategies are promising for accelerating drug discovery against challenging targets like fusion proteins.

PhD – Senior

35 - COL4A1 variants as a novel cause of Congenital Anomalies of the Kidney and Urinary Tract (CAKUT)

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Background: Congenital anomalies of the kidney and urinary tract (CAKUT) are the leading 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 (Kitzler, Hum Genet, 2019). COL4A1 forms a heterotrimer with COL4A2 and is an extracellular matrix component. Pathogenic variants in COL4A1 are associated with a range of diseases, including eye defects, brain small-vessel disease, and systemic defects. However, no CAKUT cases linked to COL4A1 mutations have been reported. Here, we investigate mechanisms underlying COL4A1 variants using human cells, and examine col4a1's role in developing zebrafish kidney.

Objectives: (1) Characterize patient-specific COL4A1 missense variants using cellular assays. (2) Explore the role of col4a1 in kidney development in zebrafish.

Results: Immunocytochemistry revealed typical COL4A1 localization in all variants, showing a perinuclear pattern. A cycloheximide chase assay demonstrated a significantly reduced half-life for several COL4A1 variants when compared to wild-type. In zebrafish, we detected col4a1 expression along the pronephros at 24 hours post-fertilization (hpf). col4a1 knockdown caused abnormal widening of the pronephric duct (PD) at 24 hpf (11.53µm vs. 9.79µm in controls, 95% CI: 0.87-2.6µm, $p<0.0001$). Histological analysis revealed disorganized tissue with cell bundling at the distal PD in col4a1 morphants. To validate the specificity of the col4a1 morphants, we knocked down gata3, a transcription factor known to cause a human CAKUT phenotype (OMIM #131320) and expressed in the zebrafish PD. gata3 knockdown caused a CAKUT-specific malformation in the PD, resembling the human renal collecting duct, from which the renal pelvis and ureters derive and most CAKUT phenotypes occur.

Conclusion: We propose a potential pathogenic mechanism for missense COL4A1 variants based on cellular assays and present a CAKUT-specific readout for an established (GATA3) and novel CAKUT candidate gene (COL4A1).

36 - Pre-clinical Evaluation of the Efficacy of Riluzole for the Treatment of RNA Polymerase III - Related Leukodystrophy in a Polr3bΔ10 Mouse Model

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Leukodystrophies are genetically inherited disorders affecting the white matter of the central nervous system, regardless of structure, molecular process, or disease progression. RNA polymerase III-related leukodystrophy (POLR3-HLD), also known as 4H due to its key clinical features of Hypomyelination, Hypodontia, and Hypogonadotropic Hypogonadism, is among the most prevalent hypomyelinating leukodystrophies. It results from biallelic pathogenic variants in genes encoding RNA Polymerase III (Pol III) subunits, including POLR3A, POLR3B, POLR1C, POLR3D, and POLR3K, leading to transcriptional defects. This disease affects previously healthy children, causing progressive disability and premature death, with no available treatment. With an urgent need for effective therapies, researchers identified Riluzole, an FDA-approved drug for amyotrophic lateral sclerosis, as a potential candidate. Riluzole partially promotes Pol III complex assembly in HEK293 cells carrying the POLR3-HLD-causing R103H mutation and enhances the heat shock response, critical for protein folding and cellular support. However, its effects remain unverified in other pathogenic variants or a more relevant disease model. This study aims to determine whether Riluzole can rescue complex assembly defects in Polr3b to mitigate POLR3-HLD phenotypes. Using the Polr3bΔ10 mouse model, which mimics key features of the disease, we assessed Riluzole's impact on oligodendrocyte precursor cells (OPCs) and mature oligodendrocytes (OLs) both in vitro and in vivo. Specifically, we examined its effects on cell proliferation, differentiation, myelination, and survival. Early results suggest that while lower doses may provide some protective effects, higher doses induce toxicity and cell death. In vivo, Riluzole treatment did not improve survival or weight gain and had no significant impact on other disease-related phenotypes, including irregular/absent dentation and hypomyelination. These findings underscore the complexity of using Riluzole as a treatment for POLR3-HLD, highlighting the need for dose optimization and alternative therapeutic strategies. This study represents a critical step in evaluating Riluzole's potential, with implications for future clinical trials.

Employee

37 - Using zebrafish to rapidly resolve variants of uncertain significance in known primary ciliary dyskinesia genes

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Introduction: Primary ciliary dyskinesia (PCD) is an autosomal recessive disease (OMIM#244400) affecting 1:7,500-1:20,000 children. Variants in PCD genes lead to dysfunctional motile cilia, which are important for clearance of mucous from the respiratory tract as well as organ laterality. Currently, 20-30% of children presenting clinical features are unable to receive molecular diagnosis due to variants of uncertain significance (VUS) in PCD genes, which require functional testing to resolve pathogenicity. Without a molecular diagnosis, patients do not have access to personalized treatment. This emphasizes the need for a quick and cost-effective method to resolve VUSs.

Aim: We propose a method using zebrafish to quickly resolve VUSs in PCD genes. We will establish phenotypes associated with PCD gene knockdown, and attempt rescue with wildtype, benign (D387E), and VUS (N255K) human dnaaf1 mRNA.

Methods: Microinjections of morpholino oligonucleotides (MO) against PCD genes, and human mRNA. mRNA in situhybridization used to assess situs inversus and hydrocephaly.

Results: We have a cohort of PCD patients with homozygous variants in nine PCD genes. Three genes (DNAAF1, DNAAF3, and DNAH1) have been previously determined to exhibit ciliary phenotypes in zebrafish. dnaaf1 mutants were previously shown to exhibit situs inversus, hydrocephaly, and perturbed otoliths, which we recapitulated by knockdown of dnaaf1 resulting in 75% of embryos exhibiting a phenotype at 24hpf. Preliminary experiments suggest that rescue of situs inversus and hydrocephaly is possible in dnaaf1 morphants with co-injection of wildtype dnaaf1 human mRNA with dnaaf1 MO reducing situs inversus from 35% to 10% and hydrocephaly from 75% to 45%. Finally, preliminary evidence shows N225K VUS mRNA is able to rescue situs inversus and hydrocephaly.

Conclusion: Here, we show preliminary evidence suggesting zebrafish can be used for rapid resolution of genetic VUS.

PhD – Senior

38 - A novel Pex16 deficient mouse model for studying and treating Zellweger Spectrum Disorder

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Introduction: Zellweger Spectrum Disorder (ZSD) is a group of autosomal recessive disorders occurring in 1 in 50 000 individuals. ZSD is caused by pathogenic variants in one of 13 PEX genes, which encode PEX proteins required for peroxisome assembly and function. Peroxisomes are organelles required for multiple vital metabolic processes, such as lipid and reactive oxygen species metabolism. PEX16 is an integral peroxisomal membrane protein required for de novo peroxisome formation. While patients with ZSD usually exhibit a range of symptoms involving multiple organ systems, mutations in PEX16 lead to a unique phenotype limited exclusively to the Central Nervous System (CNS), including gait and motor abnormalities. To better understand disease pathophysiology and develop treatments for this form of ZSD, we generated a novel Pex16 deficient mouse model.

Methods and results: We generated a postnatal conditional full-body $Pex16^{-/-}$ mouse using the tamoxifen-inducible cre-mediated recombination system at 4 weeks of age. We detected decreased Pex16 transcript and protein levels in brain. We also detected abnormal peroxisome metabolite levels (elevated very long chain fatty acids and reduced plasmalogen lipids) in blood, brain and liver. These mice developed corneal inflammation (keratitis) 2-5 weeks post tamoxifen administration. Based on the other postnatal inducible peroxisome disease model (Pex5), we expect a functional phenotype to appear after 5 months post gene inactivation. At 5 months post Pex16 inactivation, there is no obvious motor anomaly and no structural changes in the brain.

Conclusion: We created a $Pex16^{-/-}$ mouse model, validated by Pex16 transcript and protein levels, severely abnormal peroxisome biomarkers and development of keratitis. By 5 months of age, clinical neurological phenotype and brain structure remain normal. To more effectively target the CNS, we will administer tamoxifen to neonates (P2-P5). Once we establish functional outcome measures, we will treat $Pex16^{-/-}$ mice with a CNS-directed PEX16 gene therapy, and assess the effects.

39 - Fetal Brain Growth: Effects of Antenatal Corticosteroids on Fetal and Neonatal Brain Development - A Pilot Study

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Background and objectives: Antenatal corticosteroids (ACS) administered to pregnant patients at risk of preterm labor reduce preterm birth related mortality and morbidity. However, in late preterm and term infants, exposure to ACS and threatened preterm labor (TPTL) may alter neurodevelopment. Our objectives are to assess the feasibility of measuring fetal and neonatal brain growth using 2D and 3D measures in fetuses exposed to ACS and TPTL compared to non-exposed fetuses.

Methods: In June 2023, we initiated a 2-year prospective observational pilot study of patients with singleton pregnancies with fetal ultrasounds every 4 weeks from 24 to 36 weeks of gestational age (GA) and a single neonatal brain ultrasound to evaluate fetal brain growth. Feasibility was evaluated according to achieving recruitment goals, adherence to ultrasound follow-up, and intra/interrater reliability of brain measures.

Results: We have thus far recruited 29 exposed and 69 non-exposed patients. Each patient that delivered received a median 4 fetal ultrasounds and 1 neonatal ultrasound. In the exposed group, of the 27 fetuses thus far delivered, 8 (30%) were delivered preterm. Intraobserver variability for fetal total intercranial and cerebellar volumes was excellent (intraclass correlation coefficient of 0.999 and 0.999, respectively). Both intraobserver and interobserver variabilities for neonaatal corpus callosal length were excellent.

Conclusions: Recruiting and serially imaging patients exposed to ACS to assess brain growth appears feasible. Ongoing recruitment and further analysis will allow us to evaluate the association between the dual exposure to ACS and TPTL and brain growth.

40 - Using Tissues from SEEG Electrodes for Presurgical Molecular Diagnosis of Focal Malformations of Cortical Development

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Focal malformations of cortical development (FMCD) are prevalent causes of drug-resistant epilepsy. Surgical resection offers treatment with seizure-free outcomes in ~50%-65% of cases. Recent breakthroughs show somatic mutations in MTOR-pathway genes or SLC35A2 underlie ~50% of FMCDs, but screening typically requires surgical tissue, limiting preoperative use. This study pioneers using tissue from SEEG electrodes—integral to presurgical investigations—to enable presurgical genetic diagnosis in FMCD patients. We aim to detect somatic mutations in SEEG-adherent cells from epilepsy patients, including known carriers and those ineligible for surgery. We hypothesize that tissue in the epileptogenic zone harbors somatic variants, enabling presurgical molecular diagnosis. We've collected SEEG electrodes, brain tissue, formalin-fixed paraffin-embedded (FFPE) block regions, and spatially correlated pathology slides from 16 epilepsy surgery patients. For somatic mutation screening, DNA from brain tissue is analyzed using our in-house FMCD panel targeting key MTOR-pathway genes, including SLC35A2. In parallel, DNA is extracted from SEEG-adherent cells using the Qiagen QIAamp DNeasy Blood & Tissue Kit (Small Blood Volumes Protocol). Bioanalyzer High-Sensitivity DNA Kit is used for quantification. DNA from electrodes within and at the margins of the epileptogenic zone will be analyzed. Our study initially validates somatic mutation detection in DNA from SEEG electrodes using droplet digital PCR (ddPCR) in patients with known mutations. In parallel, ddPCR variant allele frequencies (VAFs) from SEEG electrodes will be quantitatively compared to those from spatially matched FFPE regions. These molecular findings will be correlated with histopathological features on stained slides to assess spatial concordance between genetic and pathological data. We will then evaluate our Next-Generation FMCD panel's ability to detect somatic mutations in SEEG electrode DNA.

This study seeks to validate SEEG electrodes as a source for presurgical genetic diagnosis in FMCD and expand diagnostics to non-surgical patients, enabling a more comprehensive approach to this complex condition.

PhD – Senior

41 - Investigating the role of sildenafil in promoting neuronal plasticity after neonatal HIE: An in-vitro study

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Introduction: Birth asphyxia, leading to hypoxic-ischemic encephalopathy (HIE), affects about 3 in 1000 live births and often causes severe neurodevelopmental impairments. While therapeutic hypothermia is standard in high-income countries, it fails in 30% of cases and has uncertain efficacy in low-resource settings. Sildenafil, with potential neuroprotective and restorative effects, shows promise in preclinical studies by reducing cell death and supporting neural survival and network development, but further research is needed.

Methods: Primary neurons at day 7 in culture (DIC 7) were exposed to 6 hours (h) of hypoxia (1% O_2) and ischemia (no glucose). Subsequently, sildenafil (150 nM) was applied for 48 h to a subset of neurons. Neuronal morphology was evaluated using immunocytochemistry for MAP2 (a dendrite marker) and Tuj1 (a neurite marker). Dendrite length, dendrite number per neuron, neurite length and neurite branch number per neuron were quantified using IMARIS software in the three experimental groups: control, hypoxia-ischemia (HI) and HI + sildenafil.

Results: At DIC 10, HI caused a substantial reduction in dendrite length (42.55±29.62µm, $p < 0.005$), dendrite number per neuron (0.66±0.80, $p < 0.005$), neurite length (40.80±17.27 µm, $p < 0.005$) and neurite branch number per neuron (1.51±1.04, $p < 0.005$), compared to the control group (respectively, 122.88±42.35 µm, 3±0.83, 216.30±81.94 µm, and 6.88±2.78 µm). Sildenafil treatment significantly improved these measures, with a significant increase in dendrite length (162.69±45.58 µm, $p < 0.005$), dendrite number per neuron (3.50±1.14, $p < 0.005$), neurite length (220.30±80.12 µm, $p < 0.005$) and neurite branch number per neuron (6±2.36, $p < 0.005$) compared to the HI group; these values were significantly different from those observed in the control group.

Conclusion: HI significantly reduced dendrite and neurite markers and structural measures. Sildenafil treatment appeared to protect against deleterious HI effects and preserved dendritic and neurite growth. These findings suggest that sildenafil has a neuroprotective effect against HI.

PhD – Senior

42 - High-throughput Screen of Acute Myeloid Leukemia Stem Cells Identifies Novel anti-LSC Compounds

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Acute myeloid leukemia (AML) is a fast-progressing blood cancer characterized by the uncontrolled proliferation of abnormal myeloid cells in the bone marrow. While relatively rare in children, approximately 40% of pediatric cases relapse after initial remission, often driven by treatment-resistant leukemic stem cells (LSCs). These LSCs necessitate more intensive therapies and represent a critical therapeutic target. However, technical limitations have historically hindered high-throughput screening efforts to discover LSC-specific vulnerabilities.

To overcome these challenges, we optimized conditions for large-scale in vitro expansion and purification of $CD34^+$ LSC-enriched fractions from the primary human AML model OCI-AML-8227. Using this platform, we performed a high-throughput screen of 11,140 compounds and identified 25 novel hits with potent anti-LSC activity, including the known LSC-targeting agent venetoclax.

Three lead compounds were validated for selective toxicity, demonstrating significantly greater effects on LSC-enriched OCI-AML-8227 cells compared to healthy hematopoietic stem and progenitor cells (HSPCs). Functional validation using colony-forming unit assays and ex vivo transplantation into immunocompromised mice confirmed that these compounds reduced leukemia-initiating potential while sparing HSPC function.

Importantly, these candidates also exhibited robust anti-LSC activity in an independent poor-prognosis model (OCI-AML-20) as well as in 10 additional intermediate- and adverse-risk AML patient samples.

To investigate mechanisms of action, single-cell RNA-sequencing of the top three candidates—two with known targets and one with an uncharacterized target—revealed shared vulnerabilities in LSCs. A recurring mechanism was the induction of oxidative stress and mitochondria dysfunction, leading to LSC differentiation and/or apoptosis.

This screen not only uncovered compounds with strong therapeutic potential, but also highlighted previously underexplored biological pathways essential for LSC maintenance—offering new avenues for targeted LSC eradication in AML.

Employee

43 - Third generation sequencing identifies altered sperm DNA methylation following long term DDT exposures in South African Vhavenda Men

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We previously reported a dose-response effect of dichloro-diphenyl-trichloroethane (DDT) on human sperm DNA methylation (DNAme), using high-throughput 5-methylcytosine capture sequencing. We reported 12,846 differentially methylated regions (DMRs), predominantly DNAme gains. Introduction of third-generation long read sequencing (LRS) allowed for substantially longer reads, with simultaneous detection of DNA/RNA modifications. LRS has been used for sequencing of entire genomes, including previously unresolvable regions. Here, we used LRS to sequence new sperm DNA samples from our previously published cohort, to assess for truly genome-wide alterations in DNAme due to DDT exposure.

DNA was extracted from pellets of a minimum of 10 million sperm from low (n=3) and high (n=3) exposure to DDT, using the Qiagen MagAttract HMW DNA Kit and sent for Oxford Nanopore (ONT) and PacBio sequencing.

LRS data was able to provide information across entire imprinting control regions of imprinted genes, showing no effect of DDT. With the ability to analyze genetic information across individual long read strands, parental haplotypes were clearly identified. When viewing differential methylation due to exposure, we initially examined regions previously found to be affected. We were able to confirm regions (e.g. SALL3) demonstrating clear gains in DNAme in sperm with increased exposure to DDT. Next, we performed differential methylation analyses on LRS data. Compared to our previous results, more DMRs were found with ONT (149,612) and PacBio sequencing (499,502), representing 11- and 39-fold increases, and evidence of haplotype differences in methylation. Losses of DNAme were predominant from our LRS analyses. Interestingly, 25% and 39% of differentially methylated regions overlapped with our previous results, using ONT and PacBio analysis, respectively.

The use of third generation LRS provided high coverage genome-wide haplotype sequencing of sperm, allowing detection of large numbers of new DNAme alterations and uncovering many loci of potential susceptibility to DDT, including those in regulatory regions.

44 - POLR3-Related Leukodystrophy: The Role of Astrocytes in Disease Pathogenesis

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POLR3-related hypomyelinating leukodystrophy (POLR3-HLD) is caused by biallelic pathogenic variants in genes encoding subunits of the RNA polymerase III. Astrocytes play a central role in maintaining central nervous system homeostasis and supporting oligodendrocyte precursor cell (OPC) development. While previous studies have shown that POLR3-HLD is associated with defects in OPC proliferation, maturation in oligodendrocytes (OLs), and myelination, the role of astrocytes in the pathogenesis of this disorder has never been explored. To investigate this, we employed siRNA-mediated knockdown of Polr3a, Polr3b, and Polr1c in primary mouse cortical astrocytes as an in vitro model.

We assessed astrocyte proliferation (Ki67), apoptosis (cleaved caspase-3), and reactivity (GFAP, C3, S100A10) under basal conditions following Polr3a, Polr3b, and Polr1c-downregulation. Across all experimental conditions, astrocytes exhibited increased proliferation, reduced apoptosis, and altered expression of reactivity markers. We then employed cytokine-induced inflammatory stimulation to shift Polr3a, Polr3b, and Polr1c-downregulated astrocytes into A1 and A2 reactive states. Our preliminary results show that under these conditions, Polr3b-downregulated astrocytes demonstrate altered expression of the inflammatory gene Il-1β.

These findings offer the first direct evidence that astrocyte dysfunction may contribute to the pathogenesis of POLR3-HLD. By expanding the focus beyond OLs, this study provides a novel glial perspective on disease mechanisms and highlights the broader role of astrocytes in POLR3-HLD. Future studies will investigate how Polr3a, Polr3b, and Polr1c-downregulated astrocytes influence OPC proliferation and maturation in co-culture systems, offering further insight into the cellular interactions that shape disease progression.

Undergraduate student - Junior

45 - Comparing the Roles of Folic Acid Versus 5-Methyltetrahydrofolate in the Prevention of Epigenetic and Congenital Abnormalities Associated with the Use of Assisted Reproduction

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Assisted reproductive technologies (ART) make up ~1-6% of live births in developed countries. Though the procedures are generally safe, ART-conceived children face a higher risk of congenital abnormalities, with evidence linking these outcomes to epigenetic dysregulation, primarily in DNA methylation (DNAme). In previous studies we showed that moderate-doses (8mg/kg, 4-fold) of the methyl donor folic acid (FA) offer a protective effect against ART-associated defects in mid-gestation mouse embryos. Through this proof-of-concept mouse study, we aim to determine whether 4-fold 5-methyltetrahydrofolate (5-mTHF), a more bioactive form of folate, offers equal or superior protection against ART-associated abnormalities compared to 4-fold FA, at the blastocyst stage and in embryonic day (E)18.5 embryos. To test this, female mice were placed on one of three specialized dietary regimens for 6 weeks prior to ART: a control diet (2mg/kg, FA), a 4-fold FA-supplemented diet, or a 4-fold 5-mTHF-supplemented diet. Preliminary results indicate that neither FA nor 5-mTHF supplementation significantly impact early pregnancy/developmental measures. Ongoing efforts include analysis of LINE-1 retrotransposon expression in cultured blastocysts to determine if up-regulation, which has been implicated in implantation failure and adverse offspring outcomes observed in ART embryos, is prevented by FA or 5-mTHF supplements. Paired E18.5 embryos and placentas are being collected for assessment of morphological abnormalities, as well as genome-wide DNAme profiling, to assess if the aberrant DNAme patterns seen at E10.5 persist at an advanced developmental stage. This study will serve as proof-of-concept for improving approaches to prenatal supplementation strategies, with a primary focus on ART-based conception.

46 - Cellular and Molecular Characterization of Focal Cortical Dysplasia using Single Nucleus RNA Sequencing

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Somatic and germline pathogenic variants in mTOR pathway genes are key drivers of Focal Cortical Dysplasia (FCD) type II. This study primarily seeks to understand how a small population of cells with mTOR-activating mutations can trigger widespread epilepsy. We aim to investigate how these somatic mutations influence gene expression in both the mutated cells and neighboring non-mutated cells.

Ultra-deep sequencing was applied to detect somatic variants in mTOR pathway genes using DNA from fresh frozen tissue of patients with histologically confirmed FCDII. To explore the cellular landscape of FCDII, single-nucleus RNA sequencing (snRNA-seq) was conducted on 12 specimens, including controls and tissue within and distant from the FCDII lesion. snRNA-seq data analysis examined differences in cell type distribution and gene expression patterns.

Sequencing of mTOR pathway genes in 37 FCDII patients identified pathogenic variants in 62.1% of cases. These somatic mutations were present at low but variable allele frequencies. From 12 specimens analyzed by snRNA-seq, we obtained high-quality transcriptomic data from an average of 11,998 nuclei, capturing the diversity of cortical cell types. Comparative analysis revealed shifts in cell type distribution across FCDII and its subtypes (FCDIIA and FCDIIB). Both FCDIIA and IIB show increased expression of inflammatory markers in microglia compared to controls. Among the three microglial clusters identified, cluster 27 shows higher expression of proinflammatory mediators, particularly in FCD IIB. Gene ontology and pathway analyses indicated upregulation of immune and phagocytic processes. Transcription factors linked to mTOR hyperactivation were also enriched in Cluster 27. Cell-cell communication analysis showed increased signaling in FCDII, with Wnt signaling specifically active from microglia to astrocytes and neurons. These findings suggest microglial activation may contribute to FCDII pathogenesis and connect mTOR dysregulation to neuroinflammation.

This study demonstrates the potential of snRNA-seq combined with advanced bioinformatics to explore the molecular and cellular landscape of cortical dysplasia. Our findings underscore the pivotal role of microglial activation and mTOR pathway dysregulation in FCDII.

Research/Medical fellow

47 - 4D-Echocardiography of RV performance and dimensions in the immediate postnatal neonatal period - a prospective study.

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Background: There is limited data on the right ventricular (RV) dimensions and function in newborns using 4D-echocardiography (echo). This imaging technique allows to measure cardiac volumes by capturing all walls of the RV throughout the cardiac cycle. Speckle-tracking echo (STE) allows to reconstruct the cardiac volumes during both contraction and filling phases. Considering the complex RV geometry, this approach may augment the evaluation of common neonatal hemodynamics conditions, such as pulmonary hypertension, congenital heart disease, or right-sided heart failure

Objective: Assess the feasibility of performing 4D-echo in newborns during the immediate postnatal period and to obtain measurements of RV function and dimensions in healthy infants within their first 48 hours of life. The secondary objective was to determine whether factors such as sex, birthweight, body surface area (BSA), body mass index (BMI), or age at echo were associated with the RV end diastolic volume (EDV).

Methods: Prospective observational study recruiting healthy newborns from the nursery at the McGill University Health Centre. Included infants were born following an uncomplicated pregnancy, with no need for resuscitation at birth or admission to the neonatal intensive care unit. RV 4D-echo was done using a Philips X7-2 xMATRIX Transducer with electrocardiogram-gating. A blinded rater, unaware of the subject's details, extracted RV dimensional and functional parameters offline using STE on a TomTec Arena software.

Results: We enrolled 51 newborns, of which 28 (55%) were male. All infants were born at term (mean of 39±1 weeks). Anthropometric measurements were within the expected range for this age group (Table 1). RV 4D-echo was successfully completed in 50 (98%) and was conducted near 24 hours of life. No significant differences were observed between those evaluated before or after 24 hours. By linear regression, RV-EDV was associated to the birthweight (Table 2; p=0.002), BSA (p=0.001), BMI (p=0.002) and end diastolic area obtained by 2D echo in the apical view (p=0.03) - Figure 1, but not to sex or time at echo.

Conclusion: We demonstrated the feasibility of assessing RV dimensions and function in neonates using 4D-echo during their transitional period. As expected, RV dimensions were associated with neonatal anthropometric parameters.

48 - Characterization of urine-derived cells (UDCs) for RNA-based diagnostics

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Background

Urine-derived cells (UDCs) are a clinically useful cell type, but have not been characterized to a complete extent. These cells can act as a source of genetic material for the diagnosis of rare disorders, offering RNA in cases where DNA-based testing does not yield results. Additionally, the collection of UDCs is not invasive. We intend to characterize UDCs through a combination of RNA sequencing and immunofluorescence.

Methods

We cultured UDCs from urine samples provided by 30 patients with osteogenesis imperfecta and 10 controls (21 females, aged 4 to 20 years), growing them in two varieties of media. A number of passages, typically two, were followed by RNA extraction using TRIzol and sequencing using an Illumina NextSeq 550 device. Data on gene expression in UDCs was compared to existing GTEx data for other cells and tissues. UDCs were also characterized using immunofluorescence, with antibody staining to detect a variety of markers.

Results

UDCs exhibited a gene expression profile most comparable to that of fibroblasts. They expressed many markers for embryonic and mesenchymal stem cells, but no markers for hematopoietic stem cells. They lacked markers for many renal and urinary tract cell types. However, they did express the parietal epithelial cell markers CLDN1, DKK3, and VCAM1 and the parietal epithelial progenitor cell markers PROM1, PAX2, and SOX9. Immunofluorescence supported the expression of CLDN1, DKK3, and VCAM1 in UDCs, as well as CD13, N-cadherin, PAX8, and SIX2.

Conclusion

Gene expression data indicates that UDCs have characteristics similar to stem cells and that they may be related to progenitor parietal epithelial cells. Work is ongoing to use RNA from UDCs to diagnose genetic causes of arthrogryposis multiplex congenita. A future goal is to transdifferentiate UDCs into myocytes to enhance our analysis of genes expressed in muscle.

Employee

49 - Exposure to Group B Streptococcus-induced chorioamnionitis alters the proteome of placental extracellular vesicles.

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IntroductionGroup B Streptococcus (GBS) is an opportunistic pathogen that can cause chorioamnionitis (CA), increasing the risk of neurodevelopmental disorders (NDDs) in offspring. The placenta facilitates maternal-fetal communication through extracellular vesicles (EVs), which may carry inflammatory molecules such as interleukin (IL)-1. While EVs play a well-established role in immune modulation, their specific contribution to GBS-induced CA remains unexplored. Understanding placental-derived EVs could clarify how IL-1 and other inflammatory factors contribute to NDDs.

MethodsUsing a rat model of GBS-induced CA, we isolated and characterized EVs from control and GBS-infected placentas via nanoparticle tracking analysis and transmission electron microscopy. Proteomic profiling was performed using mass spectrometry, followed by pathway analysis. Cytokine levels were quantified via ELISA.

ResultsGBS-infected placentas exhibited calcification and increased weight, while fetal weight decreased. Proteomic analysis revealed distinct EV profiles, with enrichment of innate immune response proteins, including alarmins (S100A8/9), complement factors, and cytokine signaling pathways. Pathway analysis identified IL-1α and IL-1β as key upstream regulators. Notably, EVs from GBS-infected males showed a 44-fold increase in intracellular IL-1β compared to controls.

Discussion These findings suggest that GBS-induced CA alters placental EV composition, particularly increasing IL-1β-associated EVs. To extend these findings beyond the placenta, we also focused on fetal brain-derived EVs to explore how IL-1 signaling may contribute to neurotoxicity via the placental-brain axis. Specifically, we also aim to assess how EVs mediate the transport of pro-inflammatory signals, including IL-1, from the placenta to the fetal brain. Given growing evidence that EVs facilitate intercellular communication between the placenta and distant fetal organs, this study seeks to elucidate their role in fetal brain inflammation following GBS exposure.

Post-doc - Senior

50 - Cancer-derived extracellular vesicles for targeted delivery of EGFRvIII siRNA to glioblastoma.

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Background: Small EVs are a heterogeneous group of lipid-bound cellular particles with the size of 50-150 nm in diameter that may act as a natural cell-to-cell delivery system. Our aim is to evaluate the tumour tropism of glioblastoma cell-derived EVs towards tumour and to harness this tropism to deliver siRNA against epidermal growth factor receptor variant III (EGFRvIII) driver in glioblastoma.

Methods: Glioma cell line (U373P) was cultured and EVs were extracted from the conditioned media using ultrafiltration/ultracentrifugation protocol. Then, EVs were labelled with fluorescent dye indocyanine green (ICG). After preparing a glioblastoma model in mice with EGFRvIII transfected U373 cells used as xenograft (U373vIII), the in vivo biodistribution was evaluated through IVIS imaging. We tested different methods for loading EGFRvIII siRNA into EVs such as passive incubation, sonication, electroporation and transfection. The efficiency of each method was evaluated by nano flowcytometry followed by uptake assays and immunoblot analysis. Eventually, the transfected EVs with siRNA were selected for intravenous injection to mice bearing U373vIII xenografts followed by measuring tumour size and the expression of EGFRvIII.

Results: ICG-labelled U373P EVs showed a preferential accumulation at the tumour site while filtration could interfere with the tropism presumably by removing the EV protein corona. Regarding the cargo loading, passive loading and sonication showed the least efficiency and electroporation showed false positive results, while transfected EVs with siRNA could reduce EGFRvIII expression in vitro and partially in vivo.

Conclusion: Although the tropism of cancer-derived EVs needs further validation, we showed some evidence of successful delivery of EGFRvIII siRNA by U373P EVs into glioblastoma cells. If the challenges regarding external loading are addressed, transfected EVs could be considered a promising tool for direct delivery of therapeutics into tumours.

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

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Type 1 diabetes (T1D) is a common autoimmune disease in children, whereas non-autoimmune monogenic forms of diabetes constitute only 3% of all diabetic cases [1]. Accurate diagnosis of monogenic diabetes can significantly influence treatment decisions, potentially eliminating the need for insulin therapy. Maturity-onset diabetes of the young (MODY), the most common form of monogenic diabetes, has traditionally been considered an autosomal dominant condition associated with 14 validated genes (OMIM #606391) leading to dense family pedigrees. However, monogenic diabetes genes may drive non-autoimmune MODY, without typical clinical presentation, neonatal onset, or autosomal dominant family history, potentially leading to misdiagnosis as T1D [2, 3, 4]. We hypothesize that these known genes, along with undiscovered autosomal recessive genes explain the diabetes onset in a proportion of non-autoimmune type 1 diabetics who may benefit from therapeutic reassignment. As part of our cross-Canada Accurate Diagnosis in Diabetes for Appropriate Management (ADDAM) clinical trial (NCT03988764), whole-exome sequencing data was acquired from 358 autoantibody-negative patients with a clinical diagnosis of T1D. Rare, protein-altering variants from known monogenic diabetes were identified, where we find 17 variants scoring high for pathogenicity inclusing 9 ABCC8, 4 HNF1A, 1 HNF4A, and 3 GCK variants. Without a dominant family history but a T1D diagnosis, these results suggest that monogenic diabetes genes can play a causal role in MODY with variable penetrance. Additionally, we find 9 biallelic WFS1 variants in individuals who do not present any clinical features of Wolfram's syndrome, indicating a broader onset of monogenic diabetes than previously thought. The motivation to investigate novel recessive forms of monogenic diabetes is clear given this evidence. This study has the potential to enhance the screening and diagnostic modalities 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.

52 - Dexamethasone is associated with Ductal Closure in Extremely Preterm Infants with Evolving Lung Disease

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Background: Dexamethasone (DEXA) is administered to premature neonates with evolving lung disease, often on mechanical ventilation. Extremely premature infants frequently have a patent ductus arteriosus (PDA), associated with bronchopulmonary dysplasia (BPD). While DEXA is widely used to prevent and treat BPD, its impact on accelerating PDA closure remains unclear. This study aimed to evaluate changes in PDA size and closure rates following DEXA administration in a population exposed to a conservative PDA management policy, hypothesizing that DEXA treatment is associated with PDA size reduction and closure. **Methodology**: This prospective observational cohort study included preterm neonates (<29 weeks gestational age [GA]) receiving DEXA for evolving BPD. Serial echocardiography was performed at seven timepoints: baseline, days 3, 7, and 14 of treatment, 1 and 2 weeks post-treatment, and 36 weeks corrected GA. PDA size was measured by a blinded evaluator at all timepoints. **Results**: From 2021-2024, 52 neonates were recruited (61% male, 79% inborn). Mean birth GA was 25.4 weeks (SD: 1.4) and mean birthweight was 757 g (SD: 192 g). Median Apgar scores were 6 (IQR: 5-7) and 8 (IQR: 6-8) at 5 and 10 minutes. The average hospitalization duration was 134 days (SD: 47). The GEE model showed a significant increase in the likelihood of PDA closure over time (timepoint coefficient: 0.47, $p < 0.001$). The random effects model indicated a decrease by 0.21 mm per timepoint ($p < 0.001$). At timepoint 1, the mean PDA size was 2.02 ± 0.70 mm, decreasing to 1.44 ± 0.64 mm by timepoint 7 (in those a remaining duct (10 patients). Most infants (97% - Figure) with an unrestrictive PDA at DEXA initiation had complete closure or a restrictive PDA pattern by 36 weeks. **Conclusion**: DEXA treatment was associated with a temporal reduction in PDA patency and size, suggesting additional benefits beyond its pulmonary effects.

Research/Medical fellow

53 - Association of Self-Reported Race and Ethnicity with Transition Readiness in Adolescents with Type 1 Diabetes

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Objectives: We examined associations of self-reported race and ethnicity with diabetes transition readiness, stigma, and self-efficacy in adolescents with type 1 diabetes (T1D) and determined whether diabetes technology modified these associations.

Methods: We conducted a cross-sectional analysis of baseline data of adolescents with T1D followed at two diabetes clinics in Ontario and Quebec, Canada, and enrolled in the Keeping in Touch trial. Self-reported race and ethnicity was determined from a survey and defined as White versus Other (Black, East Asian, Indigenous, Latino, Middle Eastern, South Asian, and Southeast Asian). Participants completed validated questionnaires regarding transition readiness (Readiness of Emerging Adults with Diabetes Diagnosed in Youth (READDY)), diabetes self-efficacy (Self-Efficacy for Diabetes Self-Management measure (SEDM)), and diabetes stigma (Barriers to Diabetes Adherence (BDA)). We calculated descriptive statistics to explore associations of race and ethnicity with outcomes. Linear and logistic regression analyses are ongoing.

Results: Of 218 adolescents with T1D, 122 (56.0%) identified as White. Continuous glucose monitor usage was similar amongst adolescents (White 111 (91.0%) and Other 86 (93.5%)), whereas insulin pump use was higher in White (82 (67.2%) versus Other (51 (55.4%)). White reported a mean ± SD READDY Navigation score of 4.2 ± 0.7, SEDM of 7.5 ± 1.6, and 71 (58.7%) reported stigma. The Other group reported READDY Navigation score of 4.0 ± 0.7, SEDM of 6.9 ± 1.4, and 70 (76.1%) reported stigma.

Conclusions: Racial and ethnic disparities may exist, particularly for diabetes self-efficacy, stigma, or pump use. If associations are confirmed using multivariate analyses, then interventions targeting these areas among racial and ethnic minority youth may improve disparities in diabetes care.

Post-doc - Senior

54 - Nodal and Cripto-1: distinct mechanisms regulate trophoblast specification in mouse pregnancy

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Introduction. Proper placentation is essential for fetal growth and development in mammals. Nodal signaling is essential to ensure proper embryo development and requires Cripto-1 co-receptor, both being expressed in the developing placenta. Notably, maternal loss of either Nodal or Cripto-1 results in defective placentation, intrauterine growth restriction and fetal loss. These findings underscore the importance of Nodal and Cripto-1 for normal placental development.

Methods. To understand the roles of Nodal and Cripto-1 in trophoblasts, we developed trophoblast-specific models using Tat-Cre recombinant protein, inducing the deletion of the floxed genes in the trophectoderm at the blastocyst stage (TE-KO). Treated embryos were then transferred into pseudopregnant mice, and implantation sites were examined at gestational days 8.5 and 10.5.

Results. TE-KO of Nodal led to a decrease in implantation sites size as well as the placental thickness, primarily due to a smaller labyrinth and accompanied by an increase in the junctional zone. Immunostaining revealed an expansion of PL+ giant cell and a decrease of TPBPA+ spongiotrophoblast/glycogen cells. TE-KO of Cripto-1 also led smaller implantation sites and placental thickness, but primarily due to a smaller junctional zone. A reduction in TPBPA+ spongiotrophoblast cells, without affecting Pcdh12+ glycogen cells was observed. A reduction in MCT1+ and Gcm1+ syncytiotrophoblasts and an increase in total area of maternal blood sinuses within the labyrinth emphasized disorganization of the placental labyrinth. Early effects on trophoblast population maintenance were witnessed at d8.5 with a marked reduction in TPBPA+ cells and trophoblast cell proliferation (PCNA) and an increase in apoptosis (TUNEL).

Discussion. As distinct phenotypes were observed, Nodal and Cripto-1 roles in placenta need to be distinguish, underlying other TGF-β-dependent or independent pathways implicating Cripto-1. Overall, our findings highlight the critical role of Nodal and Cripto-1 in regulating key aspects of placental development, including trophoblast differentiation, cellular specification, and structural organization.

55 - Early Biomarkers for Gestational Diabetes

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Gestational diabetes mellitus (GDM) affects approximately 14% of pregnancies worldwide, with an increasing prevalence. Diagnosis typically occurs between 24 and 28 weeks of gestation following two failed oral glucose tolerance tests. However, earlier detection and intervention have been shown to reduce adverse pregnancy outcomes and neonatal care requirements. **This study aims to identify novel biomarkers for earlier GDM risk stratification by analyzing plasma samples collected before diagnosis.**

We used a high-throughput, multiplex protein biomarker analysis produced by Olink on plasma samples from the first and second trimester of pregnancy from 3 control patients and 3 patients later on diagnosed with GDM. Three proteins were found differentially expressed in the second trimester but only OPG (osteoprotegerin) was found differentially expressed within the first trimester. OPG has been suggested to play a compensatory role in metabolic disturbances associated with GDM, representing a potential biologically relevant biomarker. ELISA analysis throughout pregnancy show that OPG levels rise throughout pregnancy trimester in both control and GDM patients (n=9), indicating that thresholds should be determined based on gestational age. To further assess OPG's potential as an earlier screening tool for GDM, plasma samples from less than 14 weeks of gestation were analyzed and a receiver-operating characteristic curve (ROC) has demonstrated OPG has a moderate discriminatory for GDM by itself (area under the ROC curve = 0.7729).

Taken together, our findings suggest that while OPG alone may not serve as a suitable standalone diagnostic marker, it could enhance early screening when combined with other biomarkers as early as 14 weeks of pregnancy. Future work will focus on obtaining and validating additional markers, through more plasma samples, to improve specificity and accuracy in identifying high-risk patients. This research holds promise for refining early screening protocols, improving patient outcomes, and potentially reducing healthcare costs associated with GDM-related complications.

56 - Associations of Maternal and Paternal Education Level with Diabetes Distress and Glycemic Levels Among Adolescents with Type I Diabetes Before Transfer to Adult Care

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Aims: We examined associations of parental education with diabetes distress, glycemic levels, and quality of life.

Methods: We conducted a cross-sectional secondary analysis of baseline data of adolescents with T1D enrolled in the Group Education Trial to Improve Transition (GET-IT) in Montreal. Primary outcome was diabetes distress assessed using the Diabetes Distress Scale for Adults with T1D (T1-DSS). Secondary outcomes were Pediatric Quality of Life (QOL) Inventory 3.2 Diabetes Module and HbA1c (%). We used linear regression models to compare outcomes between parental education groups 1) father without university, 2) mother without university, 3) neither parent with university versus 4) both parents with university degrees.

Results: Of 184 adolescents with T1D: 88 (47.8%) male, mean (SD) age: 16.86 years (0.24), diabetes duration: 7.25 years (4.38), HbA1c: 8.16% (1.55), 39 adolescents (21.2%) had elevated diabetes distress (T1DDS ≥ 3), total T1-DDS score was 2.36 (0.78) and total Pediatric QOL score was 71.03 (13.74). There was no evidence of an association between parental education and diabetes distress; father without university (unadjusted β; 95% CI: 0.16; −0.16 to 0.48), mother without university (0.33; −0.05 to 0.71) or neither parent with university (0.20; −0.07 to 0.47) versus both parents with university (reference group). There was no evidence of an association between parental education and secondary outcomes (HbA1c or QOL).

Conclusion: Approximately 1 in 5 adolescents with T1D experienced elevated diabetes distress. There was no association between parental education and adolescent glycemic stability or diabetes-related QOL. Future studies will explore if modifiable factors such as parental involvement in their adolescent's health and their T1D knowledge are more relevant than their level of education in reducing diabetes distress.

Research/Medical fellow

57 - Association between maternal height and pregnancy outcomes or complications and cesarean delivery rate.

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Background: Maternal height has been proposed as a potential factor influencing pregnancy outcomes, yet its effects remain underexplored. Previous literature suggests that shorter maternal height may be associated with higher cesarean section rates and increased risk of cephalopelvic disproportion. This study investigates the association between maternal height and obstetrical and neonatal outcomes.

Methods: A single-center, retrospective study was conducted on deliveries at the McGill University Health Center (MUHC) between January 1st and December 31st, 2022. Inclusion criteria were women aged ≥ 18 years with recorded maternal heights and singleton pregnancies. Maternal height was categorized, with 150 cm used as the cut-off point.

Results: Out of 2834 deliveries during the study period, 1608 met the inclusion criteria. Maternal height of 150 cm or shorter was significantly associated with higher rates of emergency cesarean section, non-reassuring fetal tracings, and gestational diabetes. Women with heights between 145-150 cm were found to be at least twice as likely to experience advanced vaginal tears (3rd or 4th degree) compared to taller women

Conclusion: Shorter maternal height, particularly below 150 cm, is associated with increased rates of emergency cesarean sections and advanced vaginal tears. These findings suggest that pregnant women with shorter stature may be at higher risk for obstetrical complications and should be counseled accordingly. Delivery in facilities with advanced obstetrical care may benefit these patients.

PhD – Senior

58 - From Imbalance to Equilibrium: Antisense Oligonucleotide Therapy Targeting Allelic Expression of PEX6 in Zellweger Spectrum Disorder

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Zellweger Spectrum Disorder (ZSD) is a recessive genetic condition caused by disease variants in genes essential for peroxisome function. Peroxisomes are crucial for metabolizing certain fats and producing others critical for brain and body development. Individuals with ZSD often experience severe symptoms, including developmental delays, vision and hearing loss. Currently, there is no cure, and treatment focuses on managing symptoms. My research aims to develop a novel treatment for ZSD patients with disease variants in the PEX6 gene. Recently, a novel group of patients was identified with a single PEX6 disease gene overexpressed due to a polymorphic secondary variant eliminating a polyadenylation signal. This overexpression leads to disease manifestation even in the presence of a healthy gene. To address this, we will utilize antisense oligonucleotide (ASO) therapy, short synthetic DNA strands, to correct the overexpression of the single PEX6 disease gene in this novel patient group. By restoring balanced gene expression, this approach should improve peroxisome function and alleviate clinical symptoms. Furthermore, over one-third of patients who are compound heterozygotes for two PEX6 disease variants are expected to exhibit increased expression of one variant dependant on phasing of the polymorphic polyadenylation signal variant. In cases where a gene encoding a partially functional PEX6 protein is underexpressed, ASO therapy will be used to restore balanced expression, potentially improving disease symptoms by increasing functional PEX6 protein production. ASO therapies offer several advantages: they can be developed more rapidly than traditional gene therapies, are safer to deliver and do not alter nuclear DNA. By testing these approaches in patient-derived cells, we aim to demonstrate that ASO therapy can correct genetic imbalances in PEX6 ZSD. This research could lead to the first targeted treatment for ZSD and provide insights into personalized therapies for other rare genetic disorders.

59 - Is Mesna Safe in Middle Ear Surgeries?

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Objective:
Cholesteatoma and tympanosclerosis are chronic middle ear conditions requiring surgical intervention. Untreated, both can lead to serious complications. Tympanosclerosis typically results in conductive hearing loss due to ossicular fixation, while cholesteatoma leads to conductive hearing loss through ossicular erosion, and may also cause facial nerve damage, labyrinthine dysfunction, and intracranial issues. Sodium 2-mercaptoethanesulfonate (MESNA), with its mucolytic properties, is utilized in these surgeries to facilitate chemical tissue dissection by breaking down pathological tissues. This study evaluated the ototoxic potential of topical 100% MESNA (powder and solution) in an animal model.

Methods:
Seventeen female albino guinea pigs were used in this experiment. Sixteen of them were randomized into two groups and underwent bilateral myringotomy. Group 1 received 100% MESNA powder in one ear and powdered boric acid (control) in the other. Group 2 received 100% MESNA solution in one ear and saline (control) in the other.

A single guinea pig underwent artificial fistula creation on the medial wall of the middle ear followed by 100% MESNA solution application.

Ototoxicity was assessed using auditory brainstem response (ABR) and scanning electron microscopy (SEM) at baseline and four weeks post-application.

Results:
No visible inflammation was observed after medication application. ABR measurements showed no significant changes between baseline and 4 weeks post-application. SEM analysis demonstrated intact inner and outer hair cells across all groups.

Conclusion:
Topical application of 100% MESNA (powder and solution forms) to the middle ear of guinea pigs did not demonstrate ototoxicity, as determined by ABR and SEM. These findings remained consistent in the presence of an artificially created fistula, suggesting potential safety in compromised middle ear environments. These findings have potential implications for the surgical management of middle ear surgeries. However, further studies with larger sample sizes and long-term follow-up are warranted to confirm these results and evaluate potential risks.

PhD – Senior

60 - Sildenafil and Brain Metabolite Recovery in Neonates with Hypoxic-Ischemic Injury

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Background: Birth asphyxia and hypoxic-ischemic encephalopathy (HIE) are leading causes of mortality and disability. Therapeutic hypothermia (TH), the only treatment in high-income countries, is often ineffective in low- and middle-income countries and does not promote repair. Treatments like enteral sildenafil, are needed to support brain recovery.

Objective: Assessing neuronal-health-related brain metabolites in healthy neonates and HIE neonates treated with TH+/-sildenafil during the first month of life.

Methods: Prospective neuroimaging study involving healthy neonates and neonates with HIE treated with TH. A subset of HIE neonates with brain injury despite TH received sildenafil from Day 2 to 9. Brain MRS were performed on days of life (DOL) 2, 10 and 30. We compared N-acetyl aspartate (NAA) concentration, NAA/Creatine (Cr), and Lactate (Lac)/NAA ratios in thalamus in neonates without injury (NoBI), HIE neonates with brain injury treated only with TH (BI+TH), and with brain injury treated with TH and sildenafil (BI+TH/S).

Results: 229 MRI scans were obtained from 12 healthy, 54 NoBI+TH, 37 BI+TH, and 19 BI+TH/S neonates. By DOL10, both brain injury groups showed significant reductions in NAA concentration and NAA/Cr ratio. Reductions persisted in the BI+TH group by DOL30, while the BI+TH/S group's values were no longer significantly different from the NoBI group. By DOL30, the BI+TH/S group also had higher NAA/Cr ratios than the BI+TH group. The Lac/NAA ratio, significantly elevated on DOL2 and DOL10 in both BI groups, was no longer significantly different by DOL30.

Conclusion: NAA concentration and NAA/Cr ratio were reduced in HIE neonates despite TH. Sildenafil appeared to promote recovery of both the concentration and the ratios.

Research/Medical fellow

61 - Predictors of early-onset sepsis and risk stratification decision making for preterm infants

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BACKGROUND: Early-onset sepsis (EOS) is a rare (<1%) but potentially catastrophic event if not treated early in infants born between $30^{0}/_{7}$ -$34^{6}/_{7}$ weeks gestational age (GA). The standard of care includes initiation of antibiotics pending culture results leading to over-exposure to antibiotics with long-term adverse outcomes and antimicrobial resistance. A risk-stratification-based algorithm could help guide antibiotic use and improve antimicrobial stewardship.

OBJECTIVE: To identify risk factors for EOS preterm neonates born $30^{0}/_{7}$ -$34^{6}/_{7}$ weeks GA and compare different risk stratification approaches in this population.

METHODS: Retrospective observational study of infants born between $30^{0}/_{7}$ -$34^{6}/_{7}$ weeks' GA admitted to the Canadian Neonatal Network Neonatal Intensive Care Units from January 1, 2018, to December 31, 2023. EOS was defined as having a positive blood and/or cerebrospinal fluid culture within 3 days of birth. A stepwise logistic regression analysis was used to identify significant risk factors and calculate adjusted odds ratios (AOR) and 95% confidence intervals (CI). Different risk groups were compared using the identified risk factors.

RESULTS: The incidence of EOS was 0.6% (119/18,756) among eligible neonates and 42% (8060) were exposed to broad-spectrum empiric antibiotics for suspect EOS. E. Coli was the most common pathogen (57%, 68/119). Significant risk factors for EOS included GA (30 vs 31-33 vs 34 weeks), duration of rupture of membranes (0 min vs 1min to 24h vs >24h), maternal fever, no labour initiation and respiratory support on admission (none vs non-invasive vs invasive). The risk-factor-based multivariate prediction model had high accuracy (AUC 0.85, 95% CI 0.82-0.89). Neonates were stratified into three risk groups for EOS: low risk (0.04%, 2/4775), moderate risk (0.42%, 35/8297) and high risk (3.21%, 67/2085).

CONCLUSIONS: The risk factor-based model approach for suspected EOS management could guide more precise and optimize antibiotic use in preterm infants born between $30^{0}/_{7}$ and $34^{6}/_{7}$ weeks GA.

PhD – Senior

62 - Associations between visuospatial memory and white matter myelination in school-aged survivors with neonatal encephalopathy treated with therapeutic hypothermia

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Background: Neonatal Encephalopathy (NE) is a severe perinatal complication and a leading cause of neonatal morbidity and mortality. Therapeutic Hypothermia (TH), which mitigates brain metabolism by reducing body temperature, is the only proven neuroprotective treatment for NE. Nevertheless, cumulative research performed in survivors of NE treated with TH (NE-TH) during the school-age years collectively supports the presence of various cognitive sequelae. For instance, visuospatial memory, corresponding to the ability to store and retrieve spatial information, is impaired in NE-TH. However, their underlying mechanism remains unknown.

Objective: This study aims to investigate whether myelin development may be an important determinant of visuospatial memory performance in school-age NE-TH children.

Methods: We assessed bundle-wise myelination in the white matter of 9-10-year-old NE-TH survivors using advanced diffusion MRI and magnetization transfer imaging (MTI). Thirty-nine major white matter bundles were segmented from whole-brain tractograms using the BundleSeg algorithm. Myelin volume fraction (MVF), axonal volume fraction (AVF), and g-ratio were derived from diffusion- and MT-weighted images. Visuospatial memory was assessed using the Rey Complex Figure test for immediate and delayed recall. ANCOVA adjusted for age, sex, and total white matter volume was used to compare memory performance and MRI metrics between groups, and multiple linear regression was used to assess structure-function associations.

Results: To date, we collected complete data in 20 NE-TH participants and 7 age- and sex-matched controls. There were no significant differences in MRI metrics or visuospatial memory between the groups. In the NE-TH group, higher MVF and AVF in the bilateral arcuate fasciculus and corpus callosum were significantly associated with better visuospatial memory performance. The g-ratio in the left cingulum was positively associated with visuospatial memory, while higher g-ratio in the same region was associated with poorer memory in the controls.

Conclusion: Preliminary results suggest that myelin development in memory-related bundles is a determinant of visuospatial memory in NE-TH survivors. Larger sample sizes will allow us to further investigate and confirm these associations.

63 - Nodal pathway regulates immunotolerance in the uterus at the pre-implantation stage

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Throughout pregnancy, the maternal immune system establishes immunotolerance by inducing regulatory T cells (Tregs), which suppress the pro-inflammatory response to sperm antigens and the semi-allogeneic fetus. An inability to establish immunotolerance has been implicated in recurrent pregnancy loss and implantation failure. Nodal, a morphogen of the transforming growth factor β (TGF-β) superfamily, has recently been suggested to play a role in establishing immunotolerance during pregnancy. The reproductive-tract specific Nodal knockout mouse model ($Nodal^{\Delta/\Delta}$) demonstrated an implantation failure rate of 50%, an abundance of pro-inflammatory cells and the absence of Tregs. We hypothesize that the absence of Tregs could explain the implantation failure in $Nodal^{\Delta/\Delta}$ and therefore could be rescued by Treg induction and/or recruitment.

Since TGF-β is known to induce a tolerogenic response by promoting Treg generation during the pre-implantation period, the uterine horns of $Nodal^{\Delta/\Delta}$ females were supplemented with 10, 25 or 50 ng of Human Recombinant TGF-β1 just prior to mating. Implantation rates were assessed on gestation days 5.5-7.5. Our preliminary results demonstrate that the administration of 10 ng of TGF-β1 increases the implantation rate of $Nodal^{\Delta/\Delta}$ females to 91% (n=10) compared to 73% in $Nodal^{\Delta/\Delta}$ -PBS/BSA controls (n=11). The average number of implantation sites in TGF-β1 supplemented $Nodal^{\Delta/\Delta}$ females was slightly reduced (6.8 in $Nodal^{\Delta/\Delta}$ vs 9 in controls), suggesting a partial rescue and/or cell toxicity.

Together, our results suggest that the low implantation rate of $Nodal^{\Delta/\Delta}$ mice can be rescued through TGF-β supplementation. Future studies will verify whether implantation rescue results from Treg induction by analyzing immune cells via flow cytometry. This will include quantifying Tregs using the FOXP3 marker in $Nodal^{\Delta/\Delta}$ control and TGF-β injected uteri before implantation. Ultimately, our study could broaden our knowledge on implantation failure mechanisms and propose possible treatments.

PhD – Senior

64 - Developmental Milestones and Mobility Status among Children with Arthrogryposis: Multicentric Cross-Sectional Study

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Background: Arthrogryposis multiplex congenita (AMC) affects children's developmental milestones and mobility. Contextual factors like contracture severity, gestational age, hospitalization, and socioeconomic status can impact these outcomes. Valid measures are needed to understand mobility function.

Objectives: This cross-sectional study aims to (1) assess the content and construct validity of 4 mobility measures (Functional Mobility Scale, Functional Ambulation Questionnaire, WeeFIM, and PROMIS) for individuals with AMC and (2) determine factors associated with child development and mobility.

Methods: Data from 398 children aged birth to 21, recruited from eight Shriners hospitals, were analyzed. Content validity was assessed via the Content Validity Index (CVI) and linking to the ICF. Correlation (r) and logistic regression were used to assess construct validity and identify factors associated with child development and mobility.

Results: Mobility measures showed acceptable content and construct validity (CVI ≥ 0.82, convergent r ≥ 0.66; divergent r ≤ 0.381). The measures were mainly linked to the activity and participation and the environmental factors domains of the ICF. The measures did not assess scooting and powered mobility concepts. Gestational age, hand contractures, NICU stay, and parental employment were significantly associated with child development ($p < 0.05$). Multivariate analysis revealed that having Distal Arthrogryposis (OR=4.217) and employed parents (OR=2.721) were associated with better home and school mobility. Conversely, knee contractures (OR=0.126) and higher pain intensity (OR=0.858) were associated with worse community mobility.

Conclusion: These findings can help clinicians identify children with AMC at risk of delayed milestones and inform researchers studying factors predicting future physical limitations.

Post-doc - Senior

65 - The why, what and how of a new classification system of gross motor functioning for arthrogryposis.

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Introduction. There is no classification system of gross motor functioning of children with arthrogryposis multiplex congenita (AMC). The Gross Motor Function Classification System for children with cerebral palsy is a widely used tool. However, its application to children with other congenital/orthopedic conditions has not been validated. There is a need for a condition-specific classification system for gross motor functioning in AMC. This study aims to develop and validate the Gross Motor Functional Classification for children and youth with AMC (GMFC-AMC). **Participants and methods.** Phase 1: A development team (n= 11; clinicians, researchers and people with lived experience) drafted the GMFC-AMC over nine remote meetings. Phase 2: Nominal groups were conducted with stakeholders (n=16) from different geographical regions to ensure applicability of GMFC-AMC levels using case vignettes. Phase 3: Delphi surveys were conducted with international experts (n=40) to achieve consensus (80% agreement) on content rating each sentence regarding relevance, comprehension and comprehensibility (1=strong disagreement, 5=strong agreement) in two rounds. **Results.** The GMFC-AMC current version includes four age groups (2-4, 4-6, 6-12, and 12-18 years) and five performance levels, incorporating qualifiers for upper limb involvement. Preliminary data using a North American AMC registry (n=400) demonstrates that walking ability varied from 1 (cannot take any steps; n=23,11.1%) to 10 (walks; n=26,12.5%); indicating that GMFC-AMC will be useful to classify gross motor functioning across performance levels. **Conclusion.** GMFC-AMC will have meaningful distinctions between levels in a group of rare musculoskeletal conditions. GMFC-AMC has the potential to enhance the comparability of research findings, as it standardizes the way motor function is reported across studies, ensuring consistency. Future steps will investigate its reliability and concurrent validity in a large cohort of children and cross-cultural adaptations.

Post-doc - Senior

66 - Automated AI-Based Scoring for Upper Limb Function in Children with Arthrogryposis Multiplex Congenita

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Background: Assessing upper limb function in children with **Arthrogryposis Multiplex Congenita (AMC) 1-21 years old** is crucial for evaluating treatment outcomes and guiding rehabilitation. The Shriners Hospital Arthrogryposis Pediatric Evaluation- Upper extremity **(SHAPE-UP) scoring system**, a standardized recorded clinical assessment tool, provides structured evaluations of upper limb movement. However, **manual scoring is time-consuming, subjective, and prone to variability**, necessitating an automated solution.

Objective: This project aims to develop a **deep learning-based AI model** to automate SHAPE-UP scoring using **video-based motion analysis**. The AI system will assess **joint movement, range of motion, and functional performance**, reducing manual effort while enhancing **scoring consistency and objectivity**.

Methods: The SHAPE-UP was developed as a performance-based, video-recorded measure of the UE using a scoping review, engagement of people with lived experience and clinicians. We will analyze **100 assessment videos** from 6 **Shriners Hospital for Children (SHC) sites**. The AI model will be trained using **convolutional neural networks (CNNs) and pose estimation algorithms** to detect and quantify upper limb movements. Key challenges include **obstructed hand views, tilted perspectives, and joint occlusion** due to overlapping limbs. Initial AI experiments will be conducted on healthy participants to refine movement tracking before applying the model to children with AMC.

Expected Outcomes: This AI-driven system is expected to:

Automate SHAPE-UP scoring, minimizing manual effort and inter-rater variability.

Improve clinical decision-making by providing objective and reproducible movement assessments.

Enhance accessibility by enabling remote assessments for AMC patients.

Conclusion: By integrating AI into **pediatric rehabilitation**, this project seeks to advance automated movement analysis, ultimately **enhancing patient care and treatment evaluation**. Future directions include **expanding AI training datasets** and exploring real-time assessment applications.

67 - Estimated Prevalence of RNA Polymerase III-Related Disorders Reveals Relative Commonality Among Leukodystrophies

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Background: RNA Polymerase III-related disorders (POLR3-RD), including hypomyelinating leukodystrophy (POLR3-HLD), result from biallelic pathogenic variants in genes encoding RNA Polymerase III (Pol III) subunits. POLR3-RD exhibits broad clinical and genetic heterogeneity, with over 380 pathogenic variants identified in more than 550 known cases. POLR3-HLD accounts for 60% of cases, making it one of the most common HLDs. **Methods:** Pathogenic variants associated with POLR3-RDs were first curated from a large patient database of more than 550 patients. All variants present in gnomAD v4 of the five major causal genes were also retrieved, filtered for coding sequence variants only. Variants were classified using ACMG guidelines, filtering out benign and likely benign variants and reevaluating variants of uncertain significance (VUS). Patients were categorized into five diagnostic groups, with POLR3-HLD encompassing the largest cohort; the remaining groups representing specific phenotypic subtypes, such as striatal variant disorders (SVD), spastic ataxia/hereditary spastic paraplegia (SA/HSP), and Treacher Collins syndrome (TCS). Allele frequencies were extracted from gnomAD v4, and cumulative carrier and disease prevalence were estimated using Hardy-Weinberg equilibrium. **Results:** A multi-modal approach to our variant selection resulted in an estimated prevalence of 0.46-2.28 per 100,000, confirming that POLR3-RDs are rare; however, they reinforce that POLR3-HLD is one of the most common HLDs. Uniquely, we utilized the Hardy-Weinberg equation to calculate prevalence from both homozygous and compound heterozygous genotypes, a critical feature of the POLR3-RD cohort, providing a reliable estimate of prevalence. Pathogenic variants with high allele frequencies were identified, revealing potential founder variants in the Quebec and other underrepresented populations. **Conclusion:** This study presents the first comprehensive estimation of POLR3-RD prevalence, underscoring its relative prevalence among leukodystrophies. Accurate prevalence data will help identify novel founder variants and better characterize underrepresented patient populations. These findings provide a foundation for therapeutic development and clinical trial design for POLR3-RDs.

Research/Medical fellow

68 - Micro-preemies and Evaluation of Right Ventricular function and Pulmonary Pressure at 4 Months Corrected Age

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Background: Extremely preterm infants (<29 weeks) are at increased risk for pulmonary hypertension (PH) and cardiac dysfunction. However, there is limited data on their post-discharge cardiac and pulmonary vascular health, especially for the infants born at the limits of viability (<25 weeks). This study aimed to evaluate right ventricular (RV) function and pulmonary pressure of these micro-preemies at 4 months corrected gestational age (cGA) and compare them to more mature extremely preterm newborns.

Methods: Prospective observational cohort study including all infants born at <29 weeks and followed at our neonatal follow-up clinic between 2018 and 2021. Infants with significant genetic conditions, congenital anomalies were excluded. Echocardiograms were performed by the research team, and RV function and pulmonary pressure were analyzed offline by a blinded expert regarding the GA at birth. Infants born at <25 weeks were compared to those born at 26-29 weeks. Statistical analyses were conducted using RStudio.

Results: A total of 64 infants were included; 15 (23%) were born at <25 weeks. Demographic and clinical information are presented in **Table 1**. Systolic pulmonary artery pressure (sPAP) was significantly elevated, while pulmonary artery acceleration time (an indicator that decreases with higher pulmonary vascular resistance) was significantly lower (**Table 2**) in infants < 25 weeks. A greater proportion of these infants had an estimated sPAP ≥40 mmHg at 4 months cGA (40% vs. 4%, p=0.01). Markers of RV performance were also decreased, with RV fractional area change (FAC) significantly lower and the E/A ratio of RV inflow (a marker of diastolic function) significantly higher. Lower GA at birth was associated with decreased RV-FAC, sPAP, and systolic/diastolic time ratio (**Table 3**). Even after adjusting for postnatal steroid exposure as an indicator of pulmonary disease, FAC and sPAP remained significantly associated with gestational age at birth (data not shown).

Conclusions: Infants born before 25 weeks' gestation demonstrated higher sPAP and lower RV function at 4 months cGA compared to those born at 26-29 weeks. Future studies should assess whether these differences persist beyond 4 months corrected age and evaluate their potential long-term consequences.