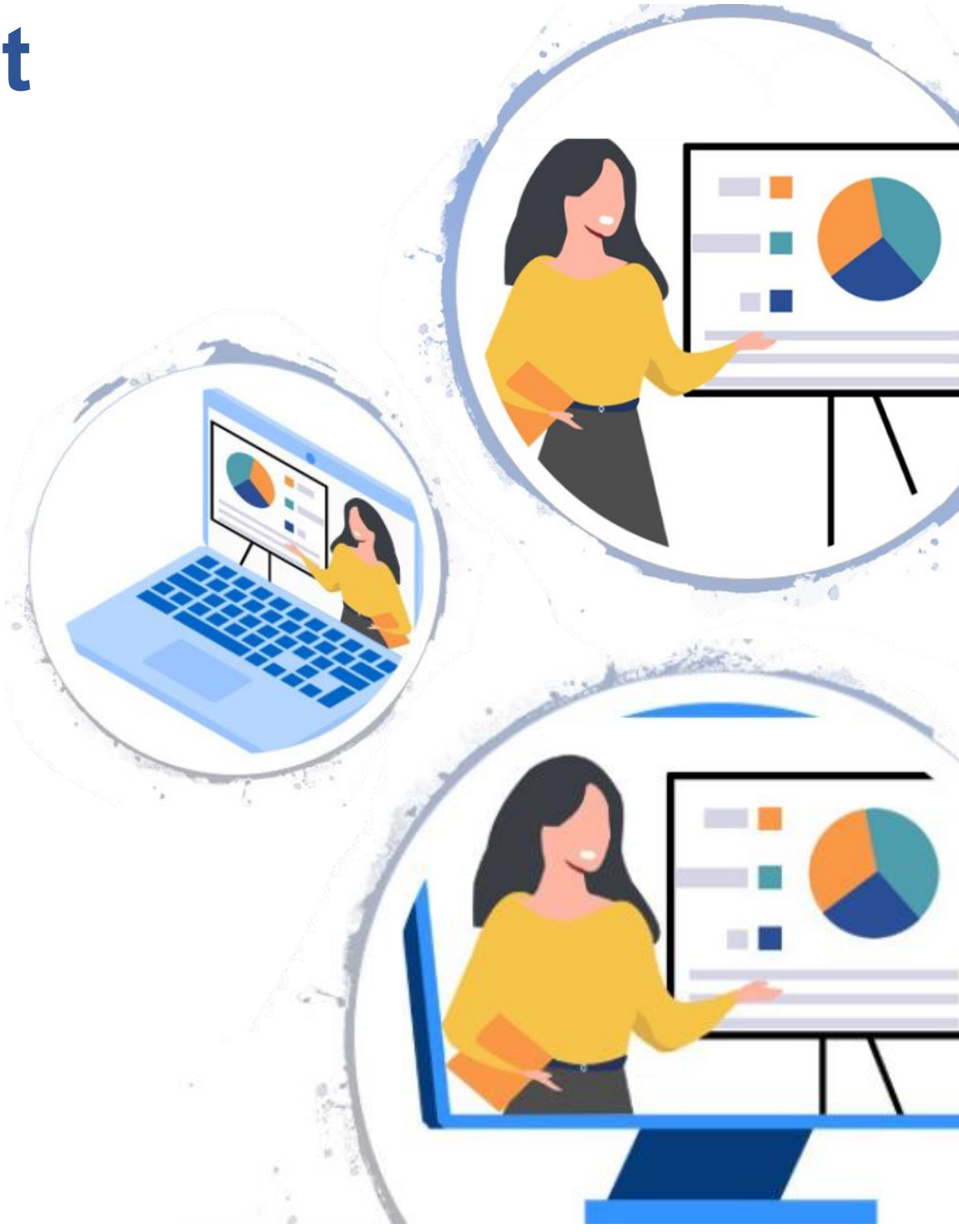
7th Annual CHHD Research Day

November 12, 2021

Booklet



Centre universitaire de santé McGill
Institut de recherche

McGill University Health Centre
Research Institute

CHHD
Child Health and Human Development

Welcome to the
7th Annual 2021 CHHD Research Day

Child Health and Human development Research Day is organized to reinforce and initiate collaborations between the program members and their guests through a virtual platform.

Please take note that all attendees, including presenters and judges should be registered prior to attending the event.

The registration will give you access to the full Fourwaves virtual poster platform that will be made available the day of the event, November 12th.

During the virtual poster sessions, attendees will be able to go through the abstracts list, see the files the presenter uploaded and join the conversation with the presenter (up to 8 people at the same time).

Registration deadline: November 11th, 5pm.

To register: https://event.fourwaves.com/chhd2021/

On the next pages, you will find:

- The Research day program including all the links
- The awards list
- A few important instructions to note during the day
- The abstracts list

If at any moment during the day, you have a question or a problem, please contact Fanny Toussaint and Martin Karam by email.

(fanny.toussaint@muhc.mcgill.ca; Martin.karam@muhc.mcgill.ca)

Please take note that you can always go back to the main Zoom meeting call and we will be there to answer your questions during the full day.

Program

Friday, November 12th, 2021 – 8:30am – 4:45pm

8:25 - 8:30	Login on Zoom: https://us06web.zoom.us/j/84218291604?pwd=SzlJRnd3ZEFsZWRkNWRQY3Vwd3VGZz09
Welcoming Remarks and CHHD Updates	
8:30 – 8:40	Dr. Daniel Dufort, CHHD Program leader
Presentation from the RI-MUHC Executive Director and Chief Scientific Officer	
8:40 - 9:15	Dr. Rhian Touyz
Oral presentations - Session 1: Chaired by Ruofan Song, CHHD Trainee committee's member	
9:20 - 10:10	**Junior Trainee Presentations**
9:20	Aliona Fezoua, Master student, Dr. Wintermark's Lab (1)
9:32	Mounya Duggal, Medical student, Dr. Altit's Lab (2)
9:44	Emily Wheeler, Master student, Dr. Polychronakos's Lab (3)
9:56	Arij Soufi, Medical student, Dr. Nakhla's Lab (4)
10:15 - 10:45	**Principal Investigator presentation**
10:15	**Dr. Catherine Goudie**, Junior Scientist , RI-MUHC **Title:** eHealth in pediatric cancer genetics
5 Minute Break	
Poster Session - Session 1 (Abstracts 9 to 30)	
10:50	Available though the event webpage, abstracts tab*: https://event.fourwaves.com/chhd2021/
10:50 – 12:15	Poster presentations
60 Minute Lunch Break	
13:15 - 13:20	Login on Zoom: https://us06web.zoom.us/j/84218291604?pwd=SzlJRnd3ZEFsZWRkNWRQY3Vwd3VGZz09
Oral presentations - Session 2: Chaired by Zoe Atsaidis, CHHD Trainee committee's member	
13:20 - 14:10	**Senior Trainee Presentations**
13:20	Maryam Rezaei, PhD student, Dr. Slim's lab (5)
13:32	Yulia Vaisbourd, Research Fellow, Dr. Foster's lab (6)
13:44	Vasikar Murugapoopathy, PhD student, Dr. Gupta's lab (7)
13:56	Sarah Palmis, Post-Doc, Dr. Brossard-Racine's lab (8)
14:15 - 14:45	**Principal Investigator presentation**
14:15	**Dr. Pia Wintermark,** Scientist, RI-MUHC **Title:** Sildenafil administration in neonates with neonatal encephalopathy: Progress so far

5 Minute Break	
Poster Session - Session 2 (Abstracts 31 to 47)	
14:50	Available though the event webpage, abstracts tab*: https://event.fourwaves.com/chhd2021/
14:50 - 16:15	Posters presentations
15 Minute Break	
Winners Announcement, Closing Remarks	
Login on Zoom: https://us06web.zoom.us/j/84218291604?pwd=SzlJRnd3ZEFsZWRkNWRQY3Vwd3VGZz09	
16:30 - 16:45	**Dr. Meranda Nakhla, CHHD Associate program leader**
****Toasts and Cheers****	

**Registration prior the event required*

***We invite all the participants to grab a glass of their favorite beverage and to discuss!*

Awards

Best junior oral presentation: 250$

Best senior oral presentation: 250$

Junior poster presentations:

First position: 250$

Second position: 175$

Third position: 100$

Senior posters presentation:

First position: 250$

Second position: 175$

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.

Good luck to all the presenters!

Tips prior to and during the day

✓ Test your camera and your audio.
To validate your video and audio setting for the poster sessions, do a pre-call test here

✓ Make sure you can **sign in** on the event website: https://event.fourwaves.com/chhd2021/

About the virtual poster platform:

Abstracts and files will be available at any time during November 12th to the people who previously registered for the event.

The virtual poster platform features will be activated only during the official poster session time.

The virtual poster platform will be available through the event website (presentations and abstracts tab).

Please consult the few links below to get more information about the virtual poster platform:

What to expect the day of the virtual poster session?

Watch a short video (3min) showing how to navigate in the virtual poster platform and join a conversation

How to get ready for a virtual poster session?

How to give your browser access to the camera and microphone

An error message says I need to allow access to the Camera and Microphone. What should I do?

During the oral presentation (Zoom):

✓ Please mute your microphone if you are not a presenter.

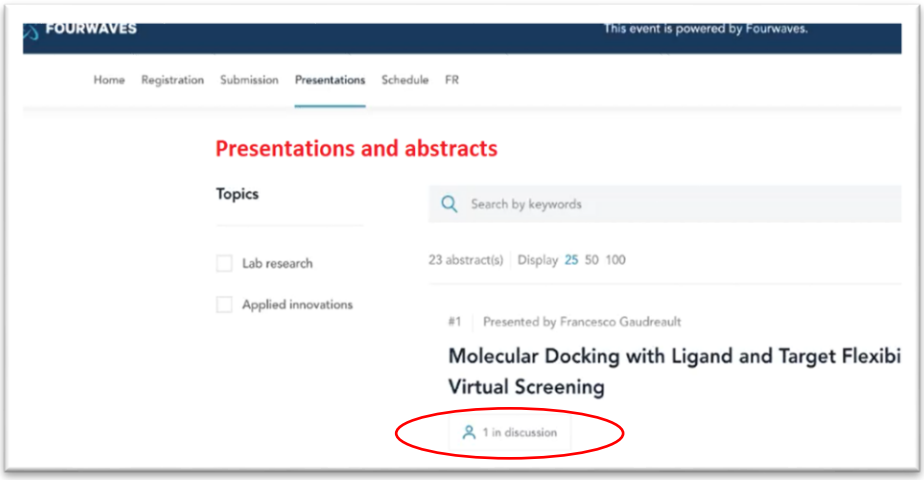
✓ Don't interrupt presenters during their presentation. Wait until the end of each presentation for questions.

✓ **Attendees are asked not to write in the chat during the Trainee Oral presentations** as the chat notification number will be used to inform the presenter of the time progression.

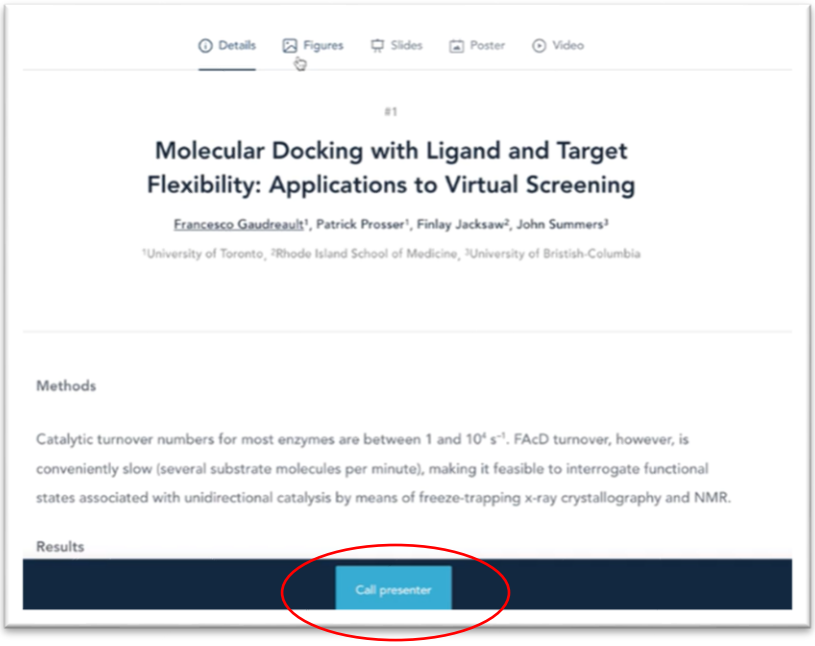
During the poster session (Fourwaves virtual poster platform):

You will have 2 options to join a conversation once you sign in your account:

1) Directly in the Presentations and abstracts tab



2) Select the abstract and click «call presenter»



When you join a conversation:

✓ Wait and see if the presenter is already speaking.

✓ Look if there is a judge in the room. If that is the case, wait until the presenter is finished their 5 minutes presentation.

✓ If you are in a conversation with a presenter and a judge enters the room, please shorten your discussion and let the judge evaluate the presenter.

Abstracts

Abstract 1 to 8: Oral presentations
Abstract 9 to 47: Poster presentations
(9 to 30: AM poster session and 31 to 47: PM poster session)

1 - Early sildenafil treatment may restore brain growth in term asphyxiated neonates with impaired deep grey matter and frontal lobe growth

Msc - Junior

Aliona Fezoua[1, 2, 3], Tristan Marcelis[1, 2, 3], Pia Wintermark[1, 2, 3]

[1]Research Institute of the McGill University Health Centre, [2]Division of Newborn Medicine, McGill University, [3]Department of Pediatrics, McGill University

Context: The impact of birth asphyxia on the substantive brain growth typically occurring in early infancy is not yet known. Sildenafil (Viagra®), unlike the current standard of care hypothermia, is both a neuroprotective and neurorestorative treatment targeting early brain repair following birth asphyxia.

Objectives: To evaluate brain growth in term asphyxiated neonates treated or not with sildenafil in addition to hypothermia within the first month of life.

Methods: Healthy neonates and asphyxiated neonates treated with hypothermia were prospectively enrolled and underwent brain magnetic resonance imaging (MRI) around days 2, 10, and 30 of life. A subset of asphyxiated neonates displaying brain injury on day 2 were randomly assigned to sildenafil treatment. Three pre-established brain metrics (deep grey matter area, bifrontal diameter, and bilateral frontal lobe height) were measured from the obtained images to evaluate brain growth at the time-points of interest. Measurements were obtained by one observer, blinded to assigned groups, and repeated three times separately.

Results: 322 neonates (12 healthy neonates and 310 asphyxiated neonates treated with hypothermia) underwent a total of 476 brain MRI scans over the first month of life. Compared to neonates without brain injury, asphyxiated neonates developing brain injury had significantly decreased deep grey matter area ($p = 0.02$), bifrontal diameter ($p = 0.005$), and bilateral frontal lobe height ($p = 0.003$) at around 1 month of life. Asphyxiated neonates developing brain injury and treated with sildenafil displayed growth measurements, for all brain metrics at around 1 month of life, that were not significantly different from neonates without brain injury.

Conclusion: Early sildenafil treatment may reduce the extent of the significantly impaired deep grey matter and frontal lobe growth in term asphyxiated neonates developing brain injury. Studying brain growth impairments in asphyxiated neonates may reveal the neurorestorative effect of sildenafil on the human neonatal brain.

2 - Association of Stigma, Diabetes Distress and Self-efficacy with Quality of Life in Adolescents with Type 1 Diabetes Preparing to Transition to Adult Care

Med student - Junior

Arij Soufi[1], Elise Mok[2], Mélanie Henderson[3], Kaberi Dasgupta[2], Elham Rahme[2], Meranda Nakhla[2, 4]

[1]Faculty of Medicine and Health Sciences, McGill University, Montreal, Qc, Canada, [2]Research Institute of the McGill University Health Centre, 5252 de Maisonneuve Ouest, Montreal, Québec, H4A 3S9, Canada, [3]Department of Pediatrics, Université de Montréal, Montreal QC, Canada, [4]Department of Pediatrics, Division of Endocrinology, McGill University Health Centre, 1001 Decarie Boulevard, Montreal, Québec, H4A 3J1, Canada

Objective: Adolescents with type 1 diabetes (T1D) face numerous challenges such as stigma that can aggravate their quality of life (QOL). Our aim was to determine whether stigma, diabetes distress and self-efficacy are associated with QOL in adolescents with T1D before the transition from pediatric to adult care.

Research Design and Methods: We conducted a cross-sectional study of adolescents (ages 16-17 years) with T1D followed at the Montreal Children's Hospital and the University Hospital Center (CHU) Sainte-Justine's pediatric diabetes centers. Participants completed validated questionnaires on stigma (defined as as an affirmative response to at least one of 3 key items on the Barriers to Diabetes Adherence [BDA] in Adolescence questionnaire), self-efficacy (Self-Efficacy for Diabetes Self-Management Measure [SEDM], score 1 to 10), diabetes distress (Diabetes Distress Scale for Adults with Type 1 Diabetes [T1-DDS], score ≥3 indicates distress) and QOL (Pediatric Quality of Life Inventory [PedsQL] 4.0 Generic Core Scale and PedsQL 3.2 Diabetes Module, score 0 to 100). We examined associations of stigma, diabetes distress and self-efficacy with QOL using multivariate linear regression models adjusted for sex, diabetes duration, socioeconomic status and HbA1c.

Results: Of 128 adolescents with T1D, 76 (59%) self-reported having diabetes-related stigma and 29 participants (22.7%) reported experiencing diabetes distress. The average on the SEDM scale was of 6.8 (± 1.6) out of 10. Those with stigma had lower diabetes-specific and general QOLscores compared with those without stigma. Stigma and diabetes distress were associated with lower diabetes-specific QOL and lower general QOL. Self-efficacy was associated with better diabetes-specific and general QOL.

Conclusion: Stigma and diabetes distress are associated with lower QOL whereas self-efficacy is associated with higher QOL in adolescents with T1D prior to transfer to adult care.

3 - The role of exonic variants in modulating translational efficiency

Msc - Junior

Constantin Polychronakos[1], Emily Wheeler[2], Erik McKelvey[3]

[1]Department of Pediatrics, McGill University, [2]Experimental Medicine, McGill University, [3]Child Health and Human Development, RI MUHC

Background: Most genetically determined traits, including disease susceptibility, depend on many genetic loci, each exerting subtle effects. Most variants involved are non-coding and assumed to affect gene expression. Transcriptional effects have been extensively studied, but there are few examples of genetic variation affecting mRNA translational efficiency. In previous work, we addressed this question by defining the effect of mRNA variants on ribosomal association (proxy for translational efficiency), transcriptome-wide, in lymphoblastoid cell lines of 200 subjects. Over 2000 variants showed significant ribosomal distribution differences between genotypes. In parallel to validation at the protein level (proteomics in progress), we undertook a computational exploration of the effect of these exonic variants on known RNA functional features.

Objectives:

Evaluate the effect of these variants on

1. miRNA binding sites.
2. RNA secondary structure (known to affect translational efficiency).
3. Linkage disequilibrium to known disease-risk variants.

Methods: RNA22 uses a pattern-based approach to find miRNA binding sites. We will implement at least one more algorithm, to reduce false positives. The RNAsnp tool will be implemented to detect local RNA secondary structure changes induced by SNPs, and methods for integrating our ribosomal QTLs with GWAS signals using LD patterns will be pursued and integrated.

Results: Preliminary results from the RNA22 miRNA target prediction tool yielded several exonic variants falling within target sites. Of over 200 significant exonic SNPs, 12 fell within predicted miRNA binding sites. Within those hits, either reference or alternative alleles created or abolished miRNA binding sites. Five variant alleles correlated with our experimental data of decreased ribosomal association when conferring a miRNA binding site. RNA secondary structure prediction and GWAS associations are currently being pursued.

Conclusion: Our computational analysis so far has demonstrated that it is possible to identify the mechanism by which exonic variation alters translation and how it affects human health.

4 - Risks and Side Effects of Diazoxide in Newborns

Mounya Duggal[1, 2, 3], Shiran Moore[1, 2, 3], Jessica Simoneau [1, 2, 3], Julia Elisabeth Von Oettingen[1, 2, 4], Guilherme Santanna[1, 2, 3], Gabriel Altit [1, 2, 3, 5]

[1] McGill University Health Centre – Montreal Children's Hospital, [2] Department of Pediatrics, McGill University, [3] Neonatology Division, [4] Pediatric Endocrinology Division, [5] Pediatric Cardiology Division.

Med student - Junior

Background: Diazoxide is a drug treating hyperinsulinemic hypoglycemia, by causing K+ efflux from beta-pancreatic cells, which inhibits insulin's release. Serious and common complications were reported: Necrotizing Enterocolitis (NEC) and Pulmonary Hypertension (PH). NEC is caused by bowel wall inflammation leading to intestinal tissue death. If inflammation persists, stool spillage in the abdomen may occur. PH presents as high blood pressure in lung's vessels and right side of the heart, leading to temporary right heart failure or mortality if not treated.

Study purpose: Better describe NEC (stage II and above) appearance in hypoglycemic and premature newborns (31+6/7 weeks GA and above) treated with diazoxide. Describe PH prevalence by echocardiography, SGA status impact on the association between NEC and diazoxide, discharge time from NICU and time of IV supplementation.

Methods: Retrospective cohort of infants admitted between January 2014 and June 2020, using local MUHC database. Clinically acquired echocardiography following diazoxide exposure were reviewed for data extraction using Syngo Dynamics workstation.

Results: Of 63 infants, 12,7% (n=8) had evidence of suspected (n=6) or confirmed (n=2) NEC. Of 36 echocardiograms, 33,3% (n=12) had evidence of PH, deemed severe (sPAP/sBP ≥ 2/3) in 19,4 % (n=7). At least 4 out of 63 neonates had a tricuspid annular plane systolic excursion (TAPSE) < 0.7 following exposure to diazoxide, indicating right ventricle dysfunction. 19 neonates had low EF measures, possibly indicating a potential LV involvement.

Conclusion: Increased incidence in PH and suspected or confirmed NEC in premature neonates with hyperinsulinemic hypoglycemia and treated with diazoxide. Diazoxide may have an adverse effect on both ventricular functions. LV involvement could be a potential driver for altered intestinal perfusion leading to NEC and post-capillary PH. Future studies should investigate the reproducibility of these results. Clinicians should be cautious when administrating diazoxide to newborns and may consider alternative medications like glucagon.

5 - A protein-truncating mutation in CCNB3 in a patient with recurrent miscarriages and failure of meiosis I

Maryam Rezaei[1], William Buckett[2], Eric Bareke[1, 3], Urvashi Surti[4], Jacek Majewski[1, 3], Rima Slim[1, 2]

PhD - Senior

[1]Department of Human Genetics, Research Institute of the McGill University Health Centre, Montreal, Quebec, Canada, [2]Department of Obstetrics and Gynecology, McGill University Health Centre, Montreal, Quebec, Canada, [3]Genome Quebec Innovation Centre, Montreal, Quebec, Canada, [4]Department of Pathology, University of Pittsburgh, Magee-Womens Hospital, Pittsburgh, Pennsylvania, USA

Recurrent miscarriage (RM) is defined by the occurrence of at least ≥2 pregnancy losses prior to 22 weeks of gestation and affects up to 5% of couples trying to conceive. In 50% of couples, no abnormalities are identified and such cases are categorized as RM of unexplained clinical etiology. To date, little is known about their genetic causes and known genes explain only a minority of cases. RM has a significant emotional impact on couples and the repetitive nature intensifies the grief experienced. A recessive missense in Cyclin B3 (*CCNB3*) has recently been shown in two sisters with RM and triploidy of maternal origin. Here we report a novel recessive *CCNB3* mutation, c.4091+1G>A, p.Val1321Glyfs*4, in a patient with 16 RM and show that one of her miscarriages is triploid digynic resulted from the failure of meiosis I.

6 - Gender differences in medication adherence among adolescent and young adult solid organ transplant recipients

Yulia Vaisbourd[1], Mourad Dahhou[2], Xun Zhang[2], Ruth Sapir-Pichhadze[2, 3, 4], Heloise Cardinal[5], Olwyn Johnston[6], Tom Blydt-Hansen[7], Lorraine Hamiwka[8], Simon Urschel[9], Janice Bissonnette[10], Mina Matsuda-Abedini[11], Jennifer Harrison[12, 13], Jeffrey Schiff[13], Veronique Phan[14], Sabina De Geest[15, 16], Upton Allen[11], Seema Mital[11], Bethany J Foster[1, 4, 17]

Research fellow - Senior

[1]McGill University, Department of Pediatrics, Montreal, [2]Research Institute of the McGill University Health Centre, Montreal, [3]Department of Medicine, McGill University, Montreal, [4]Department of Epidemiology, Biostatistics and Occupational Health, McGill University, Montreal, [5]Centre de Recherche du Centre Hospitalier de l'Université de Montréal (CHUM), Montreal, [6]Department of Medicine, University of British Columbia, Vancouver, [7]Department of Pediatrics, University of British Columbia, Vancouver, BC, Canada, [8]Department of Paediatrics, Cumming School of Medicine, University of Calgary, Calgary, [9]Department of Pediatrics, University of Alberta, Edmonton, [10]School of Nursing, University of Ottawa, Ottawa, [11]Department of Pediatrics, The Hospital for Sick Children and the University of Toronto, [12]Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, ON, Canada, [13]Multi-Organ Transplant Program, Toronto General Hospital, Toronto, ON, Canada, [14]CHU Ste-Justine, Université de Montréal, Montréal, [15]Department Public Health, Institute of Nursing Science, University of Basel, Basel, Switzerland, [16]Academic Center of Nursing and Midwifery, Department of Primary Care and Public Health, KU Leuven, Leuven, Belgium, [17]Research Institute of the McGill University Health Centre,

Background: Gender differences in adherence to immunosuppressive medications may play a role in the higher graft failure rates that have been observed in young female than male kidney and heart transplant recipients. However, prior work showed better electronically-monitored adherence in females than males, but poorer adherence in females based on standard deviation (SD) of tacrolimus levels. We aimed to compare immunosuppressive medication adherence assessed by self-report and by tacrolimus SD between male and female solid organ transplant recipients

Methods: This multicenter prospective cohort study of prevalent kidney, liver, and heart transplant recipients 14-25 y assessed adherence 3 times (0, 3, 6 months) using the BAASIS self-report tool. At each visit, participants were classified as adherent if they missed no doses in the prior 4 weeks. Standard deviation (SD) of tacrolimus trough levels (6mo before to 6mo after the first visit) was also assessed; a SD <2.0 was classified as adherent. We used multivariable mixed effects logistic regression accounting for repeated measures within participants and clustering by program. Models were adjusted for age, medication insurer and time since transplantation.

Results: At baseline, 68% of the 150 males (median age 20.4y, IQR 17.2-23.3) and 74% of the 120 females (19.8y, IQR 17.1-22.7) were adherent by self-report, whereas 70% of males and 58% of females were adherent by tacrolimus SD. Across all visits, males were significantly less likely to be adherent than females by self-report (OR 0.36, 95%CI 0.18-0.73) but more likely to be adherent by tacrolimus SD (OR 2.15, 95%CI 1.23-3.77).

Conclusion: Females show better self-reported adherence than males but greater variability in tacrolimus levels. Higher tacrolimus variability among females may contribute to previously observed higher graft failure rates in females than males, but factors other than medication adherence may influence SD of tacrolimus levels.

7 - The role of Odd-skipped relate 1 in bladder development and disease

Vasikar Murugapoopathy[1], Philippe Cammisotto[2], Abubakr Mossa[2], Lysanne Campeau[2], Indra Gupta[3, 4]

PhD - Senior

[1]Department of Human Genetics, McGill University, [2]Lady Davis Institute of the Jewish General Hospital, McGill University, [3]Department of Pediatrics, McGill University, [4]Research Institute of the McGill University Health Centre

The bladder is a hollow sac that expands up to 4 times its size when full. Bladder expansion can only occur if the bladder mesenchyme differentiates to form the collagen-rich lamina propria and the smooth muscle. Osr1 is a transcription factor that is required for development of the foregut, heart, and kidneys. We found that Osr1 mRNA is expressed in the mesenchyme and epithelium throughout bladder development. Osr1 is a downstream target of Sonic Hedgehog which is the primary regulator of mesenchyme differentiation in the bladder. We found that *Osr1*$^{-/-}$ embryos exhibit delayed differentiation and a reduction in smooth muscle at embryonic day (E)14 and E15.5, respectively. Osr1$^{-/-}$ mice do not survive past E15.5, with most dying around E12, therefore, we studied the phenotypes of *Osr1*$^{+/-}$ mice. Although newborn *Osr1*$^{+/-}$ mice did not show decreased smooth muscle, they did have a decrease in vimentin-positive fibroblasts in the lamina propria, and this was accompanied by decreased collagen I and collagen III as seen by sirius red staining and western blotting. This suggests that Osr1 also plays a role in differentiation of fibroblasts that produce the collagen of the lamina propria. We determined if the loss of collagen correlated with abnormal bladder function in adult *Osr1*$^{+/-}$ and wild-type mice. *Osr1*$^{+/-}$ mice had decreased bladder capacity and voided more frequently. Interestingly, *Osr1*$^{+/-}$ mice had increased collagen deposition in the muscle layer, which is seen during bladder injury. Our data suggests that Osr1 is a critical regulator of bladder mesenchyme differentiation in both the lamina propria and the smooth muscle layers during development and in injury.

Funding: Fonds de recherche du Québec Santé, La Fondation du Grand défi Pierre Lavoie

8 - Altered cerebellar volumes in youth born very preterm.

Sarah Palmis[1], Kaitlyn Easson[1], Aurélie Bussy[2], Guillaume Gilbert[3], May Khairy[4], Christine Saint-Martin[5], Mallar M. Chakravarty[2, 6, 7], Marie Brossard-Racine[1, 8, 9]

Post-doc - Senior

[1]1. Advances in Brain and Child Health Development Research Laboratory, Research Institute of the McGill University Health Centre, Montreal Quebec, Canada,, [2]2. Computational Brain Anatomy Laboratory, Cerebral Imaging Centre – Douglas Mental Health University Institute, Verdun Quebec, Canada,, [3]3. MR Clinical Science, Philips Healthcare, Markham Ontario, Canada, [4]4. Department of Pediatrics, Neonatal Follow-Up Program, Division of Newborn Medicine, Montreal Children's Hospital, McGill University Health Centre, Montreal Quebec, Canada, [5]Department of Medical Imaging, Division of Pediatric Radiology, Montreal Children's Hospital, McGill University Health Centre, Montreal Quebec, Canada, [6]6. Department of Psychiatry, McGill University, Montreal Quebec, Canada, [7]7. Department of Biological and Biomedical Engineering, McGill University, Montreal Quebec, Canada, [8]8. School of Physical and Occupational Therapy, McGill University, Montreal Quebec, Canada, [9]9. Department of Pediatrics, Division of Neonatology, Montreal Children's Hospital, McGill University Health Centre, Montreal Quebec, Canada

Background: Every year in Canada, more than 4500 children are born very premature (VPT) (≤32 gestational weeks) and are at high risk to present with neurodevelopmental disorders. Premature exposure to the extrauterine environment disrupts typical cerebellar development, a region of the brain involved many motor, cognitive and behavioral functions. Disrupted cerebellar development is thought to underly many neurodevelopmental disorders. Previous studies have established that individual born VPT overall have smaller cerebellar size. However, no study to date evaluated the presence of regional volumetric alterations as potential biomarker of developmental deficits in youth born VPT.

Aims: Therefore, this study aims to compare regional cerebellar volumes, as determined by quantitative MRI, between adolescents and young adults born VPT and healthy matched peers.

Methods: 51 youth born VPT, and 53 term-born control (16-27 years old) underwent a brain MRI to acquire a high-resolution anatomical image. The cerebellum of each participant was segmented into 26 subregions using MAGeTbrain Segmentation Algorithm, and regional volumes were extracted. Cerebellar volumes were compared between the two groups using ANCOVA with total brain volume and socio-economic status as covariates.

Results. Although total cerebellum was not statistically different between the two groups, regional analyses identified significant volume reductions in the corpus medullare white matter and bilateral anterior cerebellum gray matter. Further analyses revealed that the observed differences in the anterior cerebellum were driven by alterations of the bilateral lobules III and IV, and in the right lobule V.

Conclusion. Youth born VPT presented with persisting cerebellar alterations primarily located in the anterior cerebellum. These alterations may be related to the frequent motor disorder observed in children born VPT, considering the functional specificity of the anterior cerebellum. Future structure-function studies are needed to confirm the clinical significance of our findings.

9 - Effects of spliceosomal mutations on brain patterning and morphogenesis

Msc - Junior

Yanchen Dong[1, 2], Marie-Claude Beauchamp[3, 4], Sabrina Alam[1, 4], Eric Bareke[1, 5], Jacek Majewski[1, 5], Loydie Jerome-Majewska[1, 3, 4, 6]

[1]Department of Human genetics, McGill University, [2]McGill University Health Centre at Glen Site, Montreal, Quebec, Canada., [3]Department of Pediatrics, McGill University, Montreal, Quebec, Canada., [4]McGill University Health Centre at Glen Site, Montreal, Quebec, Canada, [5]McGill University and Génome Québec Innovation Centre, Montreal, QC, Canada., [6]Department of Anatomy and Cell Biology, McGill University, Montreal, Quebec, Canada.

The major spliceosome consists of U1, U2, U5, and U4/U6 small nuclear ribonucleoprotein (snRNPs), and each snRNP has distinct and sequential roles during the mRNA splicing process. Mutations in the core components of the spliceosome are associated with brain and neurological defects. The goal of this study is to examine the role of three splicing factors, SNRPB, SF3B4, and EFTUD2, in brain patterning and morphogenesis, and whether or not they are required in the neural tube or neural crest cells for brain development. Previously, we have identified brain defects associated with the mutation of these spliceosomal components in the neural tube and neural crest cells. Structures derived from the midbrain and hindbrain region, such as the diencephalon, pons, and cerebellum, were found to be absent in E12.5 and E14.5 mutant embryos. In this study, we aim to use mutant mouse models to identify shared transcripts and pathways disrupted by mutations in these spliceosomal genes. Through RNA-seq analysis, we found a few upregulated core spliceosomal genes that might act to compensate for our spliceosomal mutant genes in disease pathways. Currently, we are working to confirm these upregulations in gene expression through RT-qPCR. Furthermore, we plan to assess the potential clinical application of our findings. We will use human embryonic stem cells (hESC) to generate human neural crest cells; shared transcripts and pathways identified in the mouse model will be compared to those found in induced human neural crest cells. Distinct spliceosomophathies are difficult to diagnose due to phenotypic overlaps. The significance of this work lies in its potential to identify a disrupted pathway shared by mutations in various splicing factors, a therapeutic alternative across multiple spliceosomopathies.

10 - Assessing the Impact of the Sex Phenotype on Sex-Biased Gene Expression in the Mouse Liver

Med student - Junior

Klara Bauermeister[1], Najla AlOgayil[1], Jose Hector Galvez [2], Qinwei Kim-wee Zhuang[1], Matthew L. Chang [3], Guillaume Bourque[1, 2], Anna K. Naumova[1, 4, 5]

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Understanding how sex differences in gene expression arise and how regulators of gene expression, such as DNA methylation, contribute to these differences is an important step to furthering comprehension of sexual dimorphism. Three groups of factors, X-linked genes, Y-linked genes, and gonadal sex hormones are the major contributors to sexual dimorphism in gene regulation. However, the extent of their contribution to sex bias in gene regulation in different tissues and the underlying mechanisms are still unclear. Recently, our lab used mice with different combinations of sex-phenotype and sex-chromosome complement to catalog sex-biased differentially expressed genes (sDEGs) and sex-biased differentially methylated regions (sDMRs) in the mouse liver and identify those dependent on sex-phenotype and those dependent on sex-chromosome complement. The goals of the follow-up study presented here were a) to test the contribution of estradiol signaling through estrogen receptor alpha (ESR1) to sex bias in gene expression in the mouse liver; and b) to determine if the effects of sex-hormone signaling pathways on liver methylation could be explained by direct binding of transcription factors to sDMRs.

We conducted RNA-seq and analysis of the transcriptomes of global ESR1 knock-out mice and their wild type littermates and showed that loss of ESR1 reduced sex-biased gene expression in both male and female-biased genes, suggesting that estradiol action through ESR1 affected both male-and female-biased DEGs, either through direct or indirect mechanisms.

Next, by intersecting whole genome bisulfite sequencing (WGBS) data from our previous study with publicly available ChIP-seq data, we demonstrate that ESR1, B-cell leukemia/lymphoma 6 (BCL6), and androgen receptor (AR) bind DNA in close proximity to sDMRs. This suggests that direct binding of TFs proximal to sDMRs is a potential mechanism through which these transcription factors regulate sex-biased DNA methylation or gene expression in mouse liver.

11 - Development and validation of LC-MS/MS method to analyze the family of sphingolipid-1-phosphate in Glycogen Storage Diseases

Msc - Junior

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Glycogen storage diseases (GSD) are a group of autosomal recessive genetic disorders caused by disruption of glycogen metabolism. Depending on the specific enzyme tissue expression and resultant accumulation of glycogen, the individual glycogen storage disorder may affect the liver, skeletal muscle, kidney and heart.

The etiology of liver adenomas and subsequent progression to hepatocellular carcinomas in GSD remains elusive. Non-alcoholic fatty liver disease (NAFLD), one of the clinical complications of GSD, develops due to underlying hepatocyte damage and chronic inflammation. Traditionally, triglycerides and cholesterols were considered as the most relevant lipids in NAFLD. More recent studies have implicated another pro-inflammatory lipid class in the onset of metabolic disturbance in steatogenesis NAFLD and GSD; the "sphingolipids". Our laboratory has developed and validated analytical methods to measure various families of sphingolipid species (ceramide, hexosylceramide, sphingomyelin, ceramide-1-phosphate, C1P) using Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS). In this study, we aim at evaluating the role of sphingolipid-1-phosphate metabolites (C1P, sphingosine-1-phosphate and sphinganine-1-phosphate) in the pathogenesis of GSD, and to investigate their role in liver complications and blood inflammation. This is clinically relevant as these sphingolipids may serve as a new biomarkers and therapeutic targets for GSD patients.

Our study has three specific research aims:

Aim 1: To develop tandem mass spectrometry methods to measure sphingolipid-1-phosphate species

Aim 2: To develop extraction methods of sphingolipid-1-phosphate from biological samples, mice liver and human serum.

Aim 3: To analyze the levels of sphingolipid-1-phosphate in the serum of GSD patients and the liver of GSD mice in order to identify whether sphingolipid-1-phosphate can be used as a therapeutic biomarker.

On the Annual CHHD Research Day, our team will be presenting the progression of our ongoing research especially focusing on aim 1 and 2.

12 - Kidney Stone Project

Msc - Junior

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Kidney stones contain calcium crystals that emerge in the urine and then aggregate to form stones. This causes severe discomfort to the patient and can damage the kidneys, especially if stones are recurring. Although, there are many environmental factors that can instigate stone formation, there are also genetic risk factors based on the higher prevalence of kidney stones in monozygotic versus dizygotic twins. The most common type of kidney stone develops from hypercalciuria, which is caused by either increased calcium excretion or decreased calcium reabsorption in the nephrons of the kidney. Claudins are a large family of transmembrane proteins that are found in the tight junctions of epithelial cells such as the nephrons. Claudins interact with each other to form various kinds of ion-specific pores that together regulate the exchange of calcium and other ions between epithelial cells.

The Gupta laboratory recruited a cohort of children and adults with recurrent kidney stones to determine if any of them had DNA sequence variants in claudin genes. We identified 16 rare or novel variants in claudin genes in the cohort. Four variants were predicted to be pathogenic. We have done functional studies on two of these variants so far by stably transfecting Madin-Darby Canine Kidney (MDCK) cells with plasmids carrying the claudin sequence variants and then using confocal imaging to determine the localization of the claudins. So far, preliminary data of one of the claudin-8 variants (Claudin-8 A94V) has shown disrupted localization to the tight junctions. These functional studies will allow us to model rare, genetic causes of kidney stones in the future. These models could be used as predictive tools to understand the likelihood of kidney stone recurrence based on genotype, especially in younger patients who lack the typical environmental risk factors.

13 - Male mice lacking peroxiredoxin 6 peroxidase or Ca2+-independent phospholipase A2 activities are infertile with high levels of lipid peroxidation and tyrosine nitration in spermatozoa

Msc - Junior

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Currently, 1/6 of couples suffer from infertility, and half of cases are caused by male infertility. Oxidative stress (net increase of reactive oxygen species (ROS)) promotes infertility by inducing lipid peroxidation, DNA damage, impairment of sperm motility and capacitation, and disruption of mitochondrial activity. 4-hydroxynonenal (4-HNE), a lipid peroxide, increases levels of superoxide anion and nitric oxide responsible for protein tyrosine nitration to impair sperm motility and capacitation. Peroxiredoxin 6 (PRDX6) peroxidase and Ca^{2+}-independent phospholipase A_2 ($iPLA_2$) activities protect spermatozoa from oxidative stress by scavenging ROS and repairing oxidized membranes respectively. Spermatozoa from infertile patients have low PRDX6 levels with impaired motility, elevated lipid peroxidation levels and DNA damage. $PRDX6^{-/-}$ mice have similar abnormal parameters, resulting in smaller litter sizes compared to wildtype mice, and were worsened by tert-butyl hydroperoxide (tBHP), an oxidative stress inducer. We hypothesize that PRDX6 peroxidase or $iPLA_2$ absence promotes subfertility due to inadequate antioxidant protection. Two-month-old male C57Bl6/J (wild-type), $PRDX6^{-/-}$, C47S and D140A (peroxidase- and $iPLA_2$-deficient) mice were treated with saline (controls) or with 60 mM tBHP/100 g BW daily for 9 days. Unsuccessful matings and litter sizes were recorded. Sperm 4-HNE, nitrotyrosine and DNA oxidation levels were quantified using immunocytochemistry. Percentages of acrosome reaction were quantified in non- and capacitated spermatozoa using Giemsa staining to determine sperm capacitation. Sperm motility was determined by CASA. Mutant males had impaired sperm motility and capacitation. Control mutant males had higher sperm 4HNE, number of unsuccessful matings and lower litter sizes compared to control wildtype mice. Treated mutant males had higher sperm nitrotyrosine levels compared to treated wildtype mice. All groups, excluding control D140A mice, had higher sperm DNA oxidation levels compared to control wildtype mice. In conclusion, PRDX6 peroxidase and $iPLA_2$ prevent lipid peroxidation and tyrosine nitration to ensure male mice fertility.

Supported by CIHR.

14 - Investigating the effects of maternal NODAL on mouse placental development and vascularization during mid-pregnancy

Msc - Junior

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NODAL, a secreted protein and a member of the transforming growth factor-beta superfamily, is known to be essential for mammalian embryonic development. NODAL is also involved in female reproductive processes such as, placentation, which is associated with the successful establishment and maintenance of pregnancy. Our previous findings show that Nodal is dynamically expressed within the uterus of mice throughout different stages of pregnancy. Our lab has also displayed implications of the relation between Nodal signaling and placentation as an absence of maternal NODAL has led to placental abnormalities and affected fetal growth. How maternal NODAL affects the developmental structures within the placenta such as maternal-fetal tissues, placental vasculature, and its association with fetal growth is still unknown. Therefore, the focus is to identify the role of maternal NODAL in placental and fetal growth during mid-gestation; a key time point where placental development begins. Through the use of a uterine-specific deletion of Nodal via the Cre-LoxP system, the developmental progress of pregnant uteri, fetal growth, and thickness of maternal-fetal tissues in the placenta from Nodal homozygous knock-out mice are significantly less compared to Nodal control mice. In addition, Nodal homozygous knockout mice display severe disorganization of both the trophoblast giant cells and spongiotrophoblast cells within the maternal-fetal interface of the placenta compared to placentas from controls. Further work has been done to investigate the vascularization within the placenta of mice in the absence of maternal NODAL, specifically the structural differences of the fetal vasculature and maternal blood spaces within the placenta of Nodal homozygous knockout and control mice. These results suggest that maternal NODAL is necessary for the structural development of the maternal-fetal tissues within the placenta to support the growth of the fetus during mid-pregnancy. Consequently, an absence of maternal NODAL can compromise maternal-fetal integrity which ultimately affects fetal growth.

15 - Development of Machine-Learning Based Methodology for Severity Score of Mild and Intermediate PBD-ZSD

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Undergraduate student - Junior

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Zellweger Spectrum Disorders (ZSD) are a group of rare, autosomal recessive, multisystemic disorders characterized by a defect in peroxisome biogenesis. ZSD presentation has a phenotypic continuum ranging from mild to severe. The mild to intermediate classifications of ZSD are not distinct categories as the disease presentations are overlapping. The lack of a robust tool to assess disease severity is a significant limitation in managing and developing treatments for this disorder. Our objective was to develop and validate a robust and quantitative severity scoring system using machine learning techniques based on data available in medical records for the body systems involved in ZSD. We established a methodology using machine learning clustering algorithms to group symptoms corresponding to mild versus intermediate severity —this clustering method extracted important textual and numeric information in the pre-existing database built as part of our natural history study on ZSD patients (NCT01668186). We restricted our analysis to ophthalmological symptoms; this was done to test our newly coded clustering algorithm on a strict subset of symptoms. Our results showed that the presence of nyctalopia was the only variable that statistically separated two groups of patients when considering strictly ophthalmological symptoms. This result was statistically relevant and showed that our methodology was robust and applicable to medical records data from other systems affected in ZSD patients. The application of this methodology will allow us to determine whether specific sets of symptoms can be used to predict mild or intermediate overall disease severity in individuals with ZSD.

16 - Neuronal Effects of Sildenafil Treatment After Hypoxic-Ischemic Encephalopathy

Msc - Junior

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Introduction: Hypoxia-Ischemia (HI) in a rat model of term neonatal encephalopathy typically leads to brain injury in the cerebrum. Treatment with sildenafil after HI was found to reduce brain injury in rat pups.

Objective: To investigate the effects of sildenafil on neurons, synapses, and axons in the hippocampus and cortex in a rat model of term neonatal encephalopathy.

Methods: HI was induced in male Long-Evans rat pups at postnatal day 10 (P10) by left common-carotid ligation followed by 2-hour exposure to 8% oxygen. Sham-operated rat pups served as the control group. 12 hours after HI, HI rat pups were randomized to receive 50mg/kg of oral sildenafil or vehicle twice daily for 7 days. Rats were sacrificed at P12, P17, or P30, and hippocampus and cortex were extracted for western blot analysis for neuronal nuclei (NeuN, late neuronal marker), anti-growth associated protein 43 (GAP43, axonal regeneration marker) and synapsin-1 (pre-synaptic marker).

Results: HI significantly decreased ($p<0.05$) the expression of NeuN at P12, 17 and P30 in the hippocampus and at P30 in the cortex and it significantly decreased the expression of GAP43 at P17 in the hippocampus. Sildenafil treatment reverted the levels of NeuN to levels not anymore significantly different than sham rats in both the hippocampus and the cortex. GAP43 levels at P12 significantly increased in the hippocampus in HI-sildenafil rats ($p<0.05$), compared to the HI-vehicle treated rats; at P17, it reverted the levels of GAP43 to levels not anymore significantly different than sham rats. Synapsin-1 expression was significantly increased at P30 in the cortex in HI-sildenafil rats compared to HI-vehicle rats ($p<0.05$).

Conclusion: HI significantly reduced the number of neurons, axons and synapses. Sildenafil plays a role in restoring neurons, axons and synapses in neonatal hypoxic-ischemic brains. Further experiments are needed to better understand its role in promoting neurogenesis.

17 - Teaching Trauma in Resource-Limited Settings: A Scoping Review of Pediatric Trauma Courses

Med student - Junior

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Purpose: Injury remains an important cause of death and disability globally, with 95% of all childhood injury deaths occurring in low and lower-middle-income countries (LMICs). Pediatric trauma training, tailored to the resources in LMICs, represents an opportunity to improve such outcomes. We explored the nature of course offerings in pediatric trauma in resource-limited settings.

Methods: Seven databases were interrogated up to June 12, 2020, to retrieve articles examining pediatric trauma training in LMICs, as defined by the World Bank, without language restrictions. Independent authors reviewed and selected abstracts based on set criteria. Data from included studies was extracted and analyzed. An adapted Critical Appraisal Skills Programme (CASP) checklist designed for cohort studies was used to assess risk of bias. The Kirkpatrick framework for Trauma Courses was applied to all included articles, a measurement of trauma course efficiency from Level I-IV (IV most efficient course).

Results: After screening 3960 articles for eligibility, 16 were included for final analysis. Course delivery methods included didactic modules, simulations, clinical mentorship, small group discussion, audits, assessment, and feedback. Knowledge acquisition was primarily assessed through pre/post-tests, clinical skills assessments, and self-assessment questionnaires. Twelve studies detailed course content, nine of which were based on the WHO Emergency Triage, Assessment and Treatment (ETAT) model, which is not specific to trauma. The other 3 studies involved locally developed pediatric trauma-focused training courses, including airway management, head trauma and cervical spine management, thoracic and abdominal trauma, orthopedic trauma, burn and wound management, and shock.

Conclusion: Despite being essential to decreasing pediatric trauma morbidity and mortality worldwide, educational programs in pediatric trauma are not a widespread reality in low-and-middle-income countries. The development of accessible and efficient pediatric trauma education programs is critical for improving pediatric trauma quality of care.

18 - The current landscape of risk assessment tools identifying pediatric patients likely to have a cancer predisposition syndrome : A scoping review

Msc - Junior

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Background: There is increasing recognition of the importance of timely diagnosis of cancer predisposition syndromes (CPSs) in pediatric cancer patients. CPS identification contributes to earlier detection of subsequent cancers and cascade testing of family members. However, many factors can impact CPS recognition, including provider experience and knowledge. A variety of risk assessment tools have been developed to aid physicians and other healthcare practitioners (HCPs) in their decision to refer a patient for CPS evaluation. We conducted a scoping review to identify the currently-available tools, categorize them, and determine which features are most suitable for the pediatric population in a clinical setting.

Methods : An exhaustive search strategy was developed with a medical librarian to systematically screen MEDLINE and EMBASE, including English and French studies published by November 2020. We searched the grey literature and contacted experts in the field of genetic counselling and oncology. Eligible studies presented and/or validated CPS risk assessment tools that used the patient's profile to determine whether they are likely to benefit from a CPS genetic evaluation.

Results : A total of 27 CPS risk assessment tools were identified, 14 of which were applicable to the pediatric population. Seven of these tools were CPS-specific, 2 were cancer-specific and 5 were categorized as general CPS tools, given their applicability to multiple CPSs and/or cancers. Fifty-seven percent (8/14) of the pediatric risk assessment tools have been internally or externally validated for clinical use.

Conclusions: A large variety of CPS risk assessment tools have been developed to help HCPs decipher which patients are likely to benefit from a genetic evaluation. Their utility is largely dependent on the clinician's goals and their patient population. Importantly, further research is needed on the accuracy and validity of these risk assessment tools in addition to their generalizability to different geographic settings and ethnic populations.

19 - Technology-Enhanced Trauma Training for Resource-Limited Settings: A Scoping Review and Feasibility Analysis of Technologies Used in Training Trauma

Med student - Junior

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Lack of trauma training contributes to the burden of trauma-related mortality and morbidity in low- and middle-income countries (LMICs), especially in pediatric trauma. Medical education technologies present an opportunity to improve trauma education in LMICs. This study reviews current technologies used in trauma training and evaluates their feasibility for use in LMICs, with the goal of creating a pediatric trauma course suitable for resource limited settings.

We conducted a scoping review of articles that evaluated the learning outcomes of technology-enhanced training modules in general trauma assessment, trauma team skills and/or any procedures covered in the Advanced Trauma Life Support (ATLS®) program. The search included seven databases. Courses in the included studies were divided by technology type and skills taught in the course. The Technology-Enhanced Learning (TEL) evaluation framework was used to systematically assess the potential feasibility of the technologies in an LMIC context.

We screened 6471 articles for eligibility and included 64. 34 (45%) articles taught general assessment, 28 (37%) taught communication skills, and 24 (32%) taught technical procedures. The most common technologies used were high-fidelity mannequins (70%), low-fidelity mannequins (18%), and virtual reality (10%). Only six articles (9%) taught pediatric trauma. Despite being effective, high-fidelity mannequins overall ranked poorly in the production, maintenance, and cost categories, being therefore poorly suited to LMICs. Overall, the technologies with the best feasibility scores were virtual simulation, digital courses and video-based debriefing, as these are easy to use and sustainable while being effective.

There is an urgent need to create pediatric trauma training courses that are adapted to LMICs. Such courses must be developed with educational technologies that optimize learning outcomes and remain feasible to use with scarce resources. Educational technologies such as virtual simulation and digital courses may be used to feasibly teach pediatric trauma in LMICs and improve patient outcomes worldwide.

20 - Withdraw

21 - Moderate folic acid supplementation in pregnant mice impairs methyl metabolism and results in transcription changes in placenta and embryonic cerebrum

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PhD - Senior

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Background: Some pregnant women have higher consumption of folic acid (FA) due to food fortification and increased vitamin supplements intake. We have shown that FA supplemented diet during pregnancy, containing 5-fold higher FA than the recommended intake for mice (5xFASD), downregulated methylenetetrahydrofolate reductase (MTHFR), altered choline/methyl metabolism and led to hyperactivity-like behavior and memory impairment in 3-week-old pups.

Aim: To determine whether the metabolic disturbances and neurobehavioral abnormalities have their origins during embryonic development.

Methods: Female C57BL/6 mice were placed on control diet (CD) or 5xFASD for a month prior to mating and maintained on the same diet until pregnancy was terminated at embryonic day 17.5. Embryonic growth was evaluated by morphology, body weight and crown-rump length. Methyl metabolites and immunoreactive MTHFR were examined in maternal and embryonic tissues. Microarray profiling and real-time qRT-PCR were used to assess differential expression of placental and cerebral genes.

Results: 5xFASD resulted in pseudo-MTHFR deficiency in maternal liver and altered choline/methyl metabolites in maternal plasma (increased methyltetrahydrofolate and decreased betaine). Altered metabolites were also observed in FASD embryos, with decreased S-adenosylmethionine:S-adenosylhomocysteine ratio and glycerophosphocholine in placenta and embryonic liver. 5xFASD led to sex-specific transcriptome profiles in placenta, with confirmed expression changes for 29 genes involved in angiogenesis, receptor biology or neurodevelopment due to diet and/or sex. Sex-dependent impact of FASD on embryonic cerebral gene expression was also demonstrated with validation of dietary expression changes for several genes involved in angiogenesis, synaptic transmission or neuronal growth and differentiation.

Conclusions: 5xFASD during pregnancy results in choline/methyl metabolic disturbances in embryonic liver and placenta, as well as placental and cerebral gene expression changes. These results may provide insight into possible mechanisms of abnormal behavior in pups, and highlight the potential deleterious consequences of moderate increases in folate intake during pregnancy.

22 - Podoplanin and Tissue factor cooperate in triggering microthrombosis in experimental glioblastoma and are released to systemic circulation as cargo of extracellular vesicles

PhD - Senior

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Background: Glioblastoma associated thrombosis is, in part, an aftermath of dysregulated cancer cell genome and epigenome. Upregulation of podoplanin by cancer cells has recently been linked to an increased risk of venous thromboembolism in glioblastoma patients. Thus, regulation of this platelet activating protein by transforming events and release from cancer cells is of considerable interest.

Aims: I. Investigate and characterize podoplanin expressing populations and evaluate the impact of oncogenic driver pathways on podoplanin expression. **II.** Investigate the potential involvement of extracellular vesicles as means for systemic PDPN dissemination. **III.** Examine the role of glioblastoma-associated and systemically disseminated podoplanin in GBM associated thrombosis.

Methods: We utilized single-cell and bulk transcriptome data mining, as well as various analytical and biochemical/molecular techniques involving pharmacological inhibitors, immunoblotting, and PCR; xenograft models in mice, immunohistochemistry and immunofluorescence, electron microscopy, density gradient fractionation, Cytoflex, and ELISA.

Results: I. Podoplanin is expressed by distinct (mesenchymal) glioblastoma cell subpopulation and downregulated by oncogenic mutations of EGFR and IDH1 genes, via changes in chromatin modifications (EZH2) and DNA methylation, respectively. **II.** Glioblastoma cells exteriorize their podoplanin and/or tissue factor as cargo of exosome-like extracellular vesicles (EVs). **III.** Glioma podoplanin-EVs activate platelets, while tissue factor-EVs weakly activate the clotting cascade. Similarly, platelet activation (PF4) or coagulation markers (D-dimer) elevation occurs in mice harboring xenografts expressing podoplanin or tissue factor, respectively. Finally, PDPN and tissue factor co-expressed by glioblastoma cells cooperatively promote tumor microthrombosis.

Conclusion: In glioblastoma distinct cellular subsets drive multiple facets of cancer-associated thrombosis and may represent targets for phenotype and cell type-based diagnosis and antithrombotic intervention. Accordingly, we suggest that the preponderance of podoplanin expression as a risk factor in glioblastoma and involvement of platelets in our glioblastoma model may merit investigating antiplatelets for potential inclusion in VTE management strategies in glioblastoma setting.

23 - Niemann-Pick Type C1 with psychiatric presentation: report of a novel variant and improvement with Miglustat, with over a decade-long clinical follow-up

PhD - Senior

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Niemann-Pick type C (NPC) is an autosomal recessive lipid storage disease caused by pathogenic variants in the genes *NPC1* or *NPC2*. NPC presents with a heterogeneous clinical picture, which includes diverse systemic and neurological signs. Therefore, the diagnosis of NPC remains a prolonged and complicated process. Recent reports demonstrate that many cases of NPC remain undetected or misdiagnosed with psychiatric diseases, ultimately leading to progressive neurodegeneration and clinical deterioration. Here, we present a patient with biallelic pathogenic variants in *NPC1,* including a novel missense variant, [c.723A>C (p.Gln241His)] and a small intronic deletion (c.3592-7_3592-3del). At disease onset, the patient presented with prominent psychiatric symptoms, which evolved into progressive neurological decline, including generalized dystonia, gait ataxia, dysarthria, and vertical supranuclear ophthalmoplegia. The clinical course of disease improved after initiation of Miglustat, an inhibitor of glycosphingolipid synthesis. Early diagnosis of NPC is important in order to initiate treatment prior to neurological deterioration. Moreover, this case emphasizes that Juvenile NPC can present as a purely psychiatric disorder and underlies the importance of a prompt diagnosis to allow patients early access to a disease modifying therapy.

24 - A TUBA1B variant causes a Tubulinopathy phenotype

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Background: Variants in the genes of the tubulin superfamily are associated with Tubulinopathies, a term encompassing a group of neurodevelopmental disorders typically characterized on brain MRI by the presence of dysmorphic basal ganglia, callosal hypodysgenesis, cerebellar hypoplasia/dysplasia and a range of malformations of cortical development. The most common tubulin gene mutated is the α-tubulin gene *TUBA1A*, whereas its homologous *TUBA1B* has not been associated yet with a human phenotype.

Methods: We recruited for exome sequencing a female patient with developmental delay and complex brain malformation including corpus callosum hypoplasia, vermis hypoplasia, small pons and dysmorphic basal ganglia, remarkably suggestive of a tubulinopathy. Previous clinical sequencing of known tubulinopathy genes was unrevealing. Cellular phenotypes were studied by expressing control or mutated TUBA1B in cell lines (U2OS cells). Live imaging, immunofluorescent staining and Fluorescence-activated cell sorting (FACS) were pursued to assess cytoskeleton morphology and cell survival.

Results: We identified a *de novo* missense variant in *TUBA1B* (NM_006082.2: c.493T>C; p.S165P) that is absent from public databases and predicted to have deleterious effect by multiple *in-silico* analysis. Our in vitro experiments revealed that while the wild type TUBA1B is incorporated into the microtubule cytoskeleton, the mutant p.S165P fails to do so, rather either aggregates or remains diffuse in the cytoplasm. Furthermore, cells overexpressing the mutant TUBA1B were prone to cell death with a significantly reduced survival time at 3 days compared to control.

Conclusion: In summary, we unravel that a mutation in TUBA1B is a novel Tubulinopathy-related disorder, thus expanding the list of tubulin genes linked to neurodevelopmental phenotypes. We provide evidence that TUBA1B variants affect microtubule cytoskeleton related functions, reflecting detrimental effects on neural proliferation and migration during human brain development.

25 - A proposal on how to systematically study patient specific COL4A1 variants in congenital anomalies of the kidney for the discovery of novel targeted therapies

PhD - Senior

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Congenital anomalies of the kidney and urinary tract (CAKUT) are the most common cause of chronic kidney disease in children. Recently, rare heterozygous missense variants in the Type IV Collagen alpha 1 gene (*COL4A1)*, were identified in 12 unrelated families with CAKUT (Kitzler *Hum Genet* 2019).

COL4A1 is a fibrous collagen protein that forms a zipper-like heterotrimer and is a primary component of the basement membrane of the extracellular matrix. Protein misfolding of COL4A1 can induce endoplasmic reticulum (ER) stress and affect monomer stability, which has been suggested as a potential pathogenic mechanism for *COL4A1* missense variants (Jeanne *Am J Hum Genet* 2012). Another potential pathomechanism is disruption of heterotrimer formation, as has been demonstrated in Alport syndrome (Suleiman *Elife* 2013).

By use of stably transfected cell models, I will study the effects of patient-specific missense variants on COL4A1 monomer stability and misfolding, by studying ER stress markers and the cellular stress responses, such as the unfolded protein response. Moreover, I will employ a split-luciferase assay to determine heterotrimer formation and stability.

Next, I will use CRISPR-Cas9 in zebrafish to study the effect of loss of *col41a* on the developing kidney and urinary tract, hypothesizing that these animal models will recapitulate the human phenotype. Zebrafish are an excellent model to study the developing kidney and urinary tract, not only because of their transparent skin and easily visualization of anatomical structures, but also due to the shared anatomical structures and genetic developmental programs.

Finally, zebrafish are also an excellent model for drug discovery experiments, since the permeability of the skin allows for application of the drugs to the ambient water and makes them highly scalable. We will first target specific pathways, affecting col4a1 folding, as well as its expression, before resorting to an unbiased screening approach using large publicly available databases.

26 - Understanding patients' perceptions of transitioning from pediatric to adult diabetes care

PhD - Senior

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Among youth with type 1 diabetes (T1D), the decline of adherence to diabetes self-care and medical follow-up during the transition from pediatric to adult care has been associated with greater morbidity and mortality. Inadequate health care support for youth during the transition care period could exacerbate psychosocial risks and difficulties that are common during emerging adulthood (ages 18-30 years) and result in adverse health outcomes. The current investigation sought to explore the perceptions of emerging adults with T1D relating to their transition to adult care. Semi-structured interviews were conducted with 33 patients with T1D following their transfer to adult care (±42.21 months) in Quebec, Canada. Data was analyzed using thematic analysis. Four key themes were identified: (1) varied perceptions of the transition from being quick and abrupt with minimal advice or information from pediatric health care providers (HCP) to more positive including a greater motivation for self-management and the transition being concurrent with the developmental period; (2) facilitating factors to the transition included informational and tangible social support from HCPs and family or friends, a positive relationship with adult HCP, and a greater ease for contacting and communicating with the clinic or HCP; (3) barriers to the transition included lack of advice or information from pediatric HCPs, loss of support from HCPs and friends or family, the separation of health care services, and a greater difficulty in making appointments with adult clinic or HCP; and (4) participants recommendations for improving the transition included increasing the length and frequency of appointments, having access to educational information, and better transition preparation from HCPs. The experiences and perceptions of emerging adults are invaluable to guide the ongoing development and improvement of transition programs for childhood-onset chronic illnesses.

27 - Thrombocytopenia and neonatal outcomes among extremely premature infants exposed to maternal hypertension

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Medical resident - Senior

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Background: Maternal hypertensive disorders (MHD) are associated with unfavorable neonatal outcomes such as intraventricular hemorrhage (IVH), bronchopulmonary dysplasia (BPD), necrotizing enterocolitis (NEC), and hematological abnormalities, including thrombocytopenia.

Methods: Retrospective cohort of infants born at <29 weeks gestational age admitted to a level IV Neonatal Intensive Care Unit (NICU) between 2015 and 2019. Outcome data collected included rates of IVH (grade 3 or 4), BPD, NEC, and death, and frequency and volume of platelet transfusion. Hypothesized predictors for developing any of these outcomes were platelet count at initial complete blood count (CBC), at 2 weeks of life, at 32 weeks and 36 weeks corrected age, and at discharge. Odds of exposure to predictors for the adverse outcomes were compared between neonates born to mothers with MHD to those without. A mixed effect model was constructed to identify markers predictive of platelet count trajectory.

Results: 298 extremely premature infants were included, 43 born to mothers with MHD. Infants exposed to MHD had a significantly higher incidence of thrombocytopenia compared to non-exposed (82% vs 31%, p<0.001), and were more likely to have received platelet transfusions (76.4% vs 45%, p<0.001). Exposed infants had a higher incidence of BPD (74% vs 54%, p=0.025). Logistic regression analysis demonstrated an association between grade 3-4 IVH and platelet count on initial CBC (OR 0.94, p=0.015), and at 36 weeks of gestation (OR 0.99, p=0.02). An association was found between BPD and platelet count at 2 weeks of life (OR 0.96, p=0.02) and 36 weeks corrected (OR 0.98, p=0.02). Mixed effect model demonstrated an association between maternal hypertension and trajectory of platelet recovery (=-94, p<0.001).

Conclusion: Extremely premature infants born to MHD have a higher incidence of thrombocytopenia and an altered trajectory of platelet recovery. This profile may contribute to the development of adverse outcomes.

28 - Psychosocial and psychophysical assessment in pediatric patients and young adults with chronic back pain: a cluster analysis

PhD - Senior

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Background: Identifying subgroups with different clinical profiles may inform tailored management and improve outcomes. The objective of this study was to identify psychosocial and psychophysical profiles of children and adolescents with chronic back pain.

Methods: One hundred and ninety-eight patients with chronic back pain were recruited for the study. Pain assessment was mainly conducted in the form of an interview and with the use of validated pain-related questionnaires assessing their psychosocial factors and disability. All patients underwent mechanical and thermal quantitative sensory tests assessing detection and pain thresholds, and conditioned pain modulation efficacy.

Results: Hierarchal clustering partitioned our patients into three clusters accounting for 34.73% of the total variation of the data. The adaptive cluster represented 45.5% of the patients and was characterized to display high thermal and pressure pain thresholds. The high somatic symptoms cluster, representing 19.2% of patients, was characterized to use more sensory, affective, evaluative and temporal descriptors of pain, more likely to report their pain as neuropathic of nature, report more functional disability, report symptoms of anxiety and depression, and report poor sleep quality. The pain- sensitive cluster, representing 35.4% of the cohort, displayed deep tissue sensitivity and thermal hyperalgesia.

Conclusions: This study identified clinical profiles of children and adolescents experiencing chronic back pain based on specific psychophysical and psychosocial characteristics highlighting that chronic pain treatment should address underlying nociceptive and non-nociceptive mechanisms.

29 - Exploring Magnetoencephalography Power Spectral Analysis for Delineation of the Epileptogenic Zone in Drug Resistant Pediatric Epilepsy

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PhD - Senior

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Introduction: Epilepsy is one of the most common neurological disorders in children but ~35% of patients do not respond to anti-epileptic drugs (AEDs). Epilepsy surgery aiming to remove the epileptogenic zone (EZ), has become the standard of care in well-selected patients. However, even with state-of-the-art presurgical evaluation tests such as 3T MRI, localizing the EZ remains a challenge in poorly defined cases (i.e., MRI is negative and/or signal abnormalities are visible but correspond to suspected pathologies which are known to extend beyond what is seen on MRI (i.e., focal cortical dysplasia)). Magnetoencephalography (MEG) has become a well-accepted component of the presurgical evaluation of focal epilepsy. Current MEG source localization of the EZ requires interictal epileptiform discharges (IEDs) and so, many MEG recordings without IEDs are deemed negative and non-contributory. We have been exploring the use of MEG spectral maps via power spectral analysis of frequency bands (i.e., delta (2-4Hz) and theta (5-7Hz)) to localize focal frequency band abnormalities (FFBAs), which does not require IEDs.

Methods: We have created MEG spectral maps, for previously acquired MEG recordings, to look for FFBAs, to see if these correspond to IED source localizations. IEDs were not included in spectral map production to avoid bias.

Results: In a preliminary review of MEG recordings in 20 pediatric drug resistant epilepsy patients, we have found that MEG spectral map FFBAs are concordant with IED source localization in 85% of cases with delta being the most reliable (75% of cases).

Conclusion: MEG spectral maps hold promise towards developing novel biomarkers to help localize the EZ without requiring the capture of epileptic activity. Further exploration of our data is required to evaluate how FFBA findings correspond to other imaging modalities, post-surgical seizure outcomes, histopathology results, and MEG spectral maps in normative control subjects.

30 - Novel mutation in TRPV4 causes familial sagittal/lambdoid non-syndromic craniosynostosis with complete penetrance and variable expressivity

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Post-doc - Senior

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Craniosynostosis, the premature fusion of one or more cranial sutures, affects 1 in 2000 children. While syndromic cases are most severe due to multisystem involvement, even single-suture, non-syndromic forms, can present a wide array of troublesome signs and symptoms including headaches, papilledema, and secondary Chiari 1 malformations. Only 2-10% of non-syndromic cases are familial, depending on which suture is affected. Here, we describe a family in which the mother had unilateral coronal craniosynostosis and her 3 children had combined sagittal/lambdoid craniosynostosis, and each affected individual presentation differently (i.e., complete penetrance with variable expressivity). Array comparative genomic hybridization found no chromosomal level changes and a gene panel of over 10,000 genes, including all craniosynostosis variants and polymorphisms, did not find a causative genetic alteration. However, whole exome sequencing identified a novel mutation in the Ca2+-dependent membrane channel, Transient Receptor Potential Vanilloid 4 (TRPV4), in all affected individuals. This is the first time that this mutation (TRPV4 variant NM_021625.4:c.496C>A, p.Leu166Met) has been found to cause craniosynostosis. The 3-dimensional protein structure of this novel Leu166Met substitution was modelled using the structure of TRPV4 from *Xenopus tropicalis* (85% sequence identity), and we found that the substitution is located in the intracellular ankyrin-repeat domain at a substantial distance from the Ca2+-dependent membrane channel domain. Therefore, because it is likely not directly influencing the channel's activity, we speculate that this mutation is altering TRPV4 activity by interfering with the binding of modulatory factors. Ongoing functional analysis will better characterize the pathophysiology of this novel "TRPV4 craniosynostosis".

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

Msc - Junior

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Background: Renal ciliopathies are the most common genetic cause of end-stage renal disease (ESRD) in the first three decades of life. Ciliopathies are caused by defects of the primary cilium, an antenna-like organelle with established mechanosensory roles crucial for organ development and maintenance. Disorders of the cilium typically present with an early-onset developmental phenotype involving multiple organs (e.g., brain, eyes, skeleton, and kidney), however, milder mutations - hypomorphic variants - have been identified in ciliopathy genes in some individuals presenting with an isolated and slowly progressive renal phenotype. Crucially, if genome-wide sequencing strategies are employed, the use of current variant classification schemes alone may not correctly identify all disease-causing variants as pathogenic.

Methods: We identified rare variants in two young adults presenting with renal failure. ACMG guidelines alone did not classify these variants as pathogenic, requiring functional validation to establish a causal genotype-phenotype relationship.

Results: Biallelic missense variants in *C2CD3* were identified in a proband with isolated renal disease. Loss-of-function mutations in *C2CD3* have previously been reported to cause a developmental ciliopathy (Orofaciodigital syndrome XIV), but no cases of isolated renal disease have been described. Using patient-derived cells, we demonstrated renal-specific ciliary defects.

Pathogenic variants in *CC2D2A* cause multi-organ ciliopathy disorders in children, with no isolated renal presentations observed to date. We identified a homozygous nonsense variant (Arg34*; not previously reported) in *CC2D2A* in a previously healthy 37-year-old male patient presenting with isolated ESRD of unknown etiology. The variant was classified as not pathogenic due to an alternate start-codon. Use of publicly available expression data showed that the truncating variant was found to be predominant in kidney-specific transcripts.

Conclusion : Rare variants in known syndromic genes cause isolated renal disease in adults and require functional analysis for disease attribution. The true genetic contribution to adult ESRD is likely an underestimate.

32 - Sphingosine 1-phosphate and Ceramide 1-phosphate Promote Human Sperm Capacitation

Msc - Junior

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Capacitation results in biochemical changes that include the production of reactive oxygen species (ROS) including superoxide anion ($O_2^{\cdot -}$) and nitric oxide ($NO^{\cdot}$), timely phosphorylation events and changes in the plasma membrane lipids content. The sperm plasma membrane is rich in sphingolipids. Sphingomyelin is the precursor of sphingosine and ceramide. The Sphingosine kinase I (SphK1) and ceramide kinase (CERK) produce sphingosine-1P (S1P) and ceramide-1P (C1P), respectively. S1P is involved in preventing apoptosis of germ cell cells during spermatogenesis and the triggering of the acrosome reaction (AR) in capacitated sperm. S1P promotes $O_2^{\cdot -}$ in neutrophils and $NO^{\cdot}$ endothelial cells. C1P stimulates $NO^{\cdot}$ production in macrophages. However, the role of S1P and C1P in sperm capacitation is unknown.

We hypothesize that S1P and C1P regulate ROS production during sperm capacitation. Our objectives are: 1) To study if S1P and C1P are required for sperm capacitation; 2) To determine the presence of S1P1 receptor (S1P1R) in human spermatozoa and whether the S1PR signaling activates phospho-proteins associated with sperm capacitation; 3) To study the role of S1P and C1P in the production of ROS during sperm capacitation.

To demonstrate whether S1P and C1P are needed during capacitation, human spermatozoa were incubated in the presence or absence of SKI-178 and NVP231 (inhibitor of SphK1 and CERK, respectively), and tyrosine phosphorylation (by immunoblotting) was determined as the hallmark marker of capacitation. The localization of the S1P1R in human spermatozoa was determined by immunocytochemistry and in sperm fractions by immunoblotting using the anti-S1P1R antibody.

Spermatozoa incubated in the presence of SKI-178 and NVP231 have shown reduced levels of tyrosine phosphorylation compared to controls, demonstrating the necessity of S1P/C1P in capacitation. S1P1R was localized to the sperm head. The determination of ROS is ongoing. These studies will provide insight into the regulation of ROS production necessary for sperm capacitation.

33 - REGULATION OF LYSOPHOSPHATIDIC ACID SIGNALING IN HUMAN SPERMATOZOA.

Msc - Junior

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The lysophosphatidic acid (LPA) signaling is important to maintain germ cell viability during spermatogenesis. We previously demonstrated that the inhibition of peroxiredoxin 6 (PRDX6) phospholipase A_2 activity promotes the sperm cell death. Exogenous addition of LPA could bypass the inhibition of the $iPLA_2$ activity. However, the presence of an active LPA signaling pathway and its regulation by kinases in mature spermatozoa is unknown.

We hypothesized that the LPA signaling is active in spermatozoa and regulated by kinases. Our objectives were: 1) To determine the presence of LPA receptors (LPAR) in human spermatozoa and whether LPAR signaling activates the PI3K/AKT pathway; and 2) To study the regulation of the LPA signaling by kinases.

Human sperm cytosolic, Triton-soluble and -insoluble fractions were prepared to determine the presence of LPAR1 and LPAR6 and location of phospho-PI3K and phospho-AKT substrates in human spermatozoa by immunoblotting using specific antibodies. Spermatozoa were incubated for 3.5h at 37°C with or without Ki16425 (LPAR1-3 inhibitor), or with H89, chelerythrine, PD98059, PP2, and Tyrphostin A47 (PKA, PKC, MEK, non-receptor (NR-PTK) and receptor type tyrosine kinases (R-PTK), respectively) to determine phosphorylation of PI3K and AKT substrates.

LPAR1 and LPAR6 were localized on the plasma membrane and LPAR1 also found in the Triton-insoluble fraction of human spermatozoa. Phospho-PI3K and phospho-AKT substrates were found in cytosolic and Triton-soluble fractions. Interestingly, most of the phospho-AKT substrates were found in the Triton-insoluble fraction. Phospho-PI3K and Phospho-AKT substrates were inhibited by Ki16425, chelerythrine and Tyrphostin A47.

In conclusion, these results suggest the presence of an active LPA pathway that is regulated by PKC and receptor type-PTK, that activates the PI3K/AKT pathway is to prevent apoptotic-like changes and maintain sperm viability. These studies will help to decipher causes of sperm dysfunction associated with male infertility.

Study supported by CIHR

34 - Abnormal Placental DNA Methylation and Gene Expression Associated with Assisted Reproduction: Early Detection and Effect of Folic Acid Supplementation

Msc - Junior

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Background: In recent studies, assisted reproductive technologies (ARTs) have been associated with adverse perinatal outcomes and imprinting disorders related to abnormal embryonic and placental development. ARTs have been shown to alter major epigenetic reprogramming events related to DNA methylation during germ cell and early embryo development. Folate contributes methyl groups for proper DNA methylation establishment and maintenance during development.

Aims: (1) To determine if DNA methylation perturbations induced by ART in pre-implantation embryos precede alterations in the expression of key genes involved in early placenta development, leading to abnormal placentation observed later in ART pregnancies. (2) To investigate the role played by folic acid (FA) supplementation in preventing these defects.

Methods: Female mice were fed diets containing different levels of FA supplementation for 6 weeks prior to natural mating or ART (superovulation, in vitro fertilization, embryo culture and transfer) and continuing throughout gestation. Embryos and placentas were collected at midgestation, and RNA-sequencing performed on placentas from E10.5 female embryos. Among the genes affected by ART, 3 candidate genes involved in early placenta development (*Phlda2, EphB2, L3mbtl1*) were chosen for analysis of DNA methylation using bisulfite pyrosequencing and gene expression using droplet digital PCR (ddPCR).

Results: We show that ART results in decreases in DNA methylation and increases in methylation variance in placentas from E10.5 and delayed female embryos at the *Phlda2* imprinted control region. This result correlates with the decrease in expression reported by RNA-sequencing. Moderate FA supplementation partially improves methylation levels in E10.5 placentas while the high dose achieves the same effect in delayed placentas. We are currently performing ddPCR on the same cohort. We propose that these epigenetic alterations will help explain ART-induced adverse phenotypes observed later in gestation.

(Supported by CIHR)

35 - Novel biallelic variants in NRROS associated with a lethal microgliopathy, brain calcifications and neurodegeneration

Msc - Junior

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Negative regulator of reactive oxygen species (NRROS, aka LRRC33) is a protein of the leucine-rich repeat family predominantly expressed by myeloid cells in the central nervous system, including microglia and perivascular macrophages. NRROS plays a multitude of roles, including negative regulation of pro-inflammatory Toll-like receptor signalling, inhibition of reactive oxygen species (ROS) production by NADPH oxidase 2 and activation of latent TGF-B1, a regulator of microglia activation and a neuron survival cue. Recently, biallelic variants in *NRROS* were identified as underlying a severe and ultra-rare form of pediatric neurodegeneration, with 9 individuals reported to date as having a presentation of intracranial calcifications, brain atrophy, reduced myelination, and refractory epilepsy.

Here, we report the case of one individual with a severe neurodegenerative phenotype in which exome sequencing identified two novel variants in *NRROS*, confirmed by Sanger sequencing. *In silico* prediction software supports both these variants as pathogenic, a missense variant that is absent from control population databases c.185T>C [p.(Leu62Pro)] and a premature termination codon c.310C>T [p.(Gln104Ter)] resulting in the loss of 85% of the protein and predicted to cause loss of function due to a truncated or absent product via nonsense-mediated decay. Pathological examination has only been done for one individual with variants in *NRROS* so far. Here, we confirm these pathological findings, including both extensive grey and white matter involvement, dystrophic calcifications, and infiltration of foamy macrophages. Further, we identify the novel finding of an ultrastructure mitochondrial abnormality on electron microscopy analysis of post-mortem tissue, expanding the pathological features of disease from NRROS deficiency.

36 - Association between reported barriers to adherence and electronically monitored adherence in kidney transplant recipients

Med student - Junior

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Background: Adolescents and young adulthood is the period of time where solid organ transplant recipients are at highest risk of graft failures. The aim of this study is to establish the association between perceived barriers to adherence, as measured using the Adolescent Medication Adherence Survey (AMBS), and the implementation phase of immunosuppressive medication adherence.

Methods: This is a secondary analysis of data from the pre-intervention 3-month run-in of the *TAKE-IT* trial a multi-centre randomized controlled trial in which adherence was monitored electronically among kidney transplant recipients 11-24y. Adherence was scored 0%, 50%, or 100% on each day of observation based on the proportion of prescribed doses taken. Standard deviation of tacrolimus trough levels for the interval 3 months before baseline to end of run-in was assessed as a secondary outcome (adherent if SD<2). Multinomial logistic regression with GEE was used to estimate the association between AMBS total score and adherence. Models were adjusted for age, race, gender, and household income. Additional models considered the association between adherence and barrier load (high if ³3 barriers), total number of barriers (items rated 4-5 on questionnaire) and AMBS sub-scale scores.

Results: Adherence data were available for 136 participants. The odds of adherence were not associated with AMBS total score (OR=1.00 [95%CI 0.98-1.02]), total number of barriers (OR=1.01 [95%CI 0.92-1.10]), barrier load (OR=1.24 [95%CI 0.78-1.99]) or any AMBS sub-scale score. There were no associations between tacrolimus SD-based adherence and AMBS total score (OR= 0.9778 [95%CI 0.9271-1.0312]) or any other outcome measures.

Conclusion: A prior study demonstrated that a high AMBS disease frustration/adolescent issues subscale score was associated with poorer adherence (assessed by self-reported adherence and drug level variability). However, no associations between AMBS total or subscale scores and medication adherence were seen in this independent data set.

37 - Epilepsy in Individuals with Periventricular Nodular Heterotopia: Defining the Clinical Phenotypic Spectrum

Msc - Junior

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Periventricular nodular heterotopia (PVNH) is among the most common congenital malformations of the brain. The clinical manifestations of PVNH are highly heterogenous, although most cases are only detected when seizures appear. Based on the existing literature, the main clinical problem for those who are affected is drug-resistant epilepsy. These studies, however, have been few and limited. The aim of our study is to better describe epilepsy patterns in a large cohort of affected individuals. Thus far, we have 65 participants in our cohort. Participants are divided into two main subgroups: 26 (40%) “PVNH only” and 39 (60%) “PVNH plus” with other cerebral or cortical malformations. Nodular heterotopias are distributed as follows: 16 (25%) single focus, 12 (18%) unilateral multiple foci or 37 (57%) bilateral multiple foci. The majority of participants with bilateral PVNH (65%) present with other cerebral malformations. Variables of interest for our study include: most common seizure types, age of seizure onset, predominant electroencephalogram patterns, incidence of status epilepticus, incidence of drop attacks and overall epilepsy course, whether epilepsy is typically self-limited with resolution over time, whether seizures are pharmacoresponsive or refractory. Statistical tests for association will be performed to determine whether specific epilepsy characteristics and responses to treatment correlate with the distribution of heterotopias and the extent of the brain malformation. Overall, our goal is to clarify the epileptology of this disorder and to provide sound recommendations for diagnostic workup and treatment to improve patient management and outcomes.

38 - Cavitating leukoencephalopathy caused by a homozygous deletion in the COA8 gene

Msc - Junior

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Context: Mitochondrial disorders are a group of clinically variable disorders collectively defined by dysfunction of the electron transport chain (ETC) in the mitochondria. Cytochrome *c* oxidase (COX) is the terminal enzyme of the ETC, responsible for catalyzing an oxidation-reduction reaction in Complex IV involving cytochrome *c* and oxygen. *COA8* is a recently identified enzyme involved in COX biogenesis and is suspected to play a role protecting the complex from oxidative stress induced degradation. Biallelic pathogenic variants in *COA8* have been associated with a biochemical deficiency in COX function, and a clinical presentation characterized by neurometabolic failure, progressive ataxia, spastic quadriparesis and in some, early death. On brain MRI, there is a typical pattern consisting of a posterior predominant cavitating leukoencephalopathy.

Objectives: To report the first pathological description and further characterization of the MRI pattern in a patient with *COA8* COX deficiency.

Methods: Retrospective medical records review, including analysis of brain MRIs and an autopsy report, was performed for a patient with a homozygous 2.5 kilobase pair deletion in *COA8*.

Results: A 4-year-old boy, previously healthy, presented with a rapidly progressive neurological deterioration resulting in death months after onset. Brain MRI revealed a distinctive pattern of cavitating leukodystrophy predominantly involving the posterior cerebral white matter. Brain pathology displayed overall white matter destruction with gliosis and infiltration by macrophages.

Conclusions: We describe the clinical presentation and autopsy findings of a deceased patient with a COX deficiency caused by a homozygous 2.5 kilobase pair deletion in the *COA8* gene. Notably, only 8 individuals have been reported with pathogenic variants in *COA8*, all with a particular MRI consisting of cavitating leukoencephalopathy. Further recognition of clinical features and the characteristic MRI pattern can help guide targeted genetic testing.

39 - Characterizing the role of Histone H3.3 K36E germline mutation in Neurodevelopment

Msc - Junior

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H3.3, the non-canonical variant of Histone 3, is subject to a variety of post translational modifications on its N—terminal tail. Somatic mutations on the H3.3 encoding genes (*H3F3A* and *H3F3B*) which result in amino acid substitutions on H3.3 tail, is responsible for different types of malignancies. However, germline mutations on H3.3 correlates with neurodevelopmental disorders in human patients. Recently, a male patient suffering from developmental delays, seizure, and craniofacial with the *H3f3A* K36E germline point mutation has been reported. H3.3K36me3 is correlated with gene activation which can be tri-methylated by the activity of SETD2 methyltransferase, and can be recognized by ZMYND11 reader.

We hypothesize that, K36E substitution may disrupt the activity of SETD2 *in-cis*, and potentially disrupt ZMYND11 binding to H3.3K36. For this project, we generated Direct-Knock-In (DKI) *H3f3a* K36E mouse model to study this mutation, and by investigating the effects of the mutation on mice behavior, we have observed, hyperactivity, anxiety, self-mutilation and in general ASD-like behaviors. Next, we will be looking at various brain populations, as well as the consequences on other tissues and organs. Furthermore, by using transcriptomic and epigenomic tools and Next-Generation_Sequencing (NGS) we will analyze the effects of this mutation on gene expression pattern and post-translational modifications, respectively. This study will give further insights into the role of K36 residue and K36E substitution in chromatin remodeling and brain neurodevelopment.

40 - Role of androgen in upregulating group B Streptococcus-induced placental innate immune response

PhD - Senior

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Group B *Streptococcus* (GBS) is a leading cause of placental infection referred to as chorioamnionitis. Chorioamnionitis is associated with an increased risk of fetal morbidities including life-long neurobehavioral impairments, such as cerebral palsy or autism, which are more prominent in males than females. The mechanisms underlying this sex difference are not fully understood. This knowledge gap raises the question of the role of sex steroids in the immune response. Our hypothesis is that androgen upregulates the placental innate immune response.

Lewis dams were injected daily from gestational day (G) 18 to G21 with corn oil (vehicle) or an androgen receptor antagonist, flutamide. On G19, dams were injected with saline (control) or GBS serotype Ia suspended in saline. The four experimental groups were: (1) vehicle/control, (2) vehicle/GBS, (3) flutamide/control, (4) flutamide/GBS. Maternal, fetal sera and placentas were collected for protein assays and *in-situ* analyses. Our results showed that flutamide counteracted the androgen effect as shown by a significant decrease in anogenital distance (AGD) of male pups on flutamide. A decrease in IL-1β, IL-6 and TNF-α concentration was observed in placentas of the flutamide/GBS group compared to the GBS group. Infiltration of polymorphonuclear (PMN) cells was reduced in both maternal and fetal placental compartments in flutamide/GBS compared to GBS group. These results show that androgens modulate the placental innate immune response by upregulating proinflammatory cytokines synthesis and PMN infiltration induced by bacterial infection. This process may contribute to the skewed sex ratio towards males observed in many developmental impairments from perinatal origin.

41 - IL-1Ra blocked IL-1□ pathway driven chorioamnionitis and neurobehaviour induced by GBS

Post-doc - Senior

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Group B Streptococcus (GBS) is one of the most common bacteria isolated in human chorioamnionitis, which is a major risk factor for preterm birth, brain injuries, neurodevelopmental disorders such as cerebral palsy and autism spectrum disorders. Despite the risk of placental inflammation induced by GBS in human, still little is known about it. Previous work in our lab showed that placental inflammation triggered by GBS significantly induces placental chemokine (CXCL-1) expression, a chemokine attracting polymorphonuclear (PMN) cells. Also triggers massive infiltration of the placenta by PMN which is the hallmark of human chorioamnionitis. Moreover, upregulates interleukin-1b (IL-1b) in the placenta and maternal/fetal blood, which is linked to a higher risk of having autism spectrum disease (ASD) and Attention-deficit hyperactivity disorder (ADHD) in human. Based on the previous finding we hypothesize that counteracting live GBS-induced placental inflammation using doses of IL-1 Receptor antagonist (IL-1Ra) prevent chorioamnionitis and brain dysconnectivity subsequent neurobehavioral impairments. In this study, we showed that administrating of 10 mg/kg/12 h of IL-1Ra treatment improved the weight gain of the GBS+IL-1Ra dams. Surprisingly, ELISA showed most of the pro-inflammatory cytokines including IL-6, TNF-a IL-1b were decreased in the placenta, maternal and fetal blood circulation of GBS+IL-1Ra treated group. Moreover, IL-1Ra treatment, showed protective effect of infiltration PMNs in GBS+IL-1Ra dams compared to GBS-exposed group. Together, these results suggest the protective effect of IL-1Ra treatment on the causal pathway associating GBS-induced IL-1b-driven chorioamnionitis, brain dysconnectivity, ASD-like, and ADHD-like behaviours.

42 - The role of the tight junction protein, Claudin-3, in tissue fusion during neural tube development

PhD - Senior

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The neural tube is the embryonic precursor to the brain and spinal cord. It begins as a flat sheet of epithelial cells; whose edges, neural folds, elevate upwards and fuse along the dorsal midline of the embryo. An estimated 300 000 babies are born with neural tube defects globally each year. Our lab found that members of the claudin protein family, found in tight junctions, are essential for neural tube development. I am looking at the role of one of the members of the claudin protein family, Claudin-3 (Cldn3). Chick embryos depleted of Cldn3 display neural tube defects, originating by a failure of neural fold fusion. We hypothesize that Cldn3 is required in apically localized tight junctions to regulate the localization of proteins involved in tissue fusion to the apical surface of the cells mediating fusion. The apical cell surfaces of neural folds in Cldn3-depleted embryos lack thread like protrusions observed on fusing neural folds of control embryos seen by scanning electron microscopy. The Cldn3-depleted embryos also display increased blebbing, detachment of the cytoskeleton from the membrane. These results suggest that features of the apical neural fold are altered in Cldn3-depleted embryos. Immunofluorescence of apical and basal cell markers demonstrated that apical-basal polarity is maintained, but the apical polarity protein, Par-3, had increased apical aggregates. Staining of N-glycoproteins also showed increased apical aggregates in Cldn3-depleted embryos, suggesting that proper apical protein localization patterns are disorganized in Cldn3-depleted embryos. Cldn3 could be mediating apical protein localization patterns through it's cytoplasmic C-terminal tail that binds to scaffolding proteins, linking the tight junction to the actin cytoskeleton, and possibly other apically expressed proteins. In the future we will perform a screen of proteins expressed during neural fold fusion to identify possible candidate proteins forming the glycoprotein mesh and/or mediating tissue fusion.

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

Post-Doc - Senior

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Glioblastoma (GBM) is an incurable form of primary astrocytic brain tumour driven by glioma stem cell (GSC) compartment closely associated with vascular niche. GSC phenotypes are heterogeneous and range from proneural to mesenchymal, the latter characterized by greater invasiveness often occurring at recurrence.

Extracellular vesicles (EVs) are spherical membrane structures that cells release to communicate with one another. These packets of molecular cargo can be taken up by various ‘recipient’ cells resulting in reprogramming of the cellular content and function.

Since endothelial cells make up the vascular network, we reasoned that in GBM, EVs mediate reciprocal tumour-endothelial interactions. We examined whether endothelial EVs exert a paracrine (angiocrine) influence on GSCs and their progeny in a manner that influences stem cell hierarchy and disease aggressiveness.

Here we show that the effects of placing conditioned media from endothelial cells over the GSCs, perturbs the ability of GSCs to form clusters. These phenotypic changes were reproduced when GSCs came in contact with EVs of primary endothelial cells (EEVs). At a molecular level, EEV exposure to proneural GSCs triggered a reduction in NOTCH1, NES and SOX2 (hallmarks of proneural GSCs), while increased expressions of mesenchymal GSC hallmarks such as CD44 and VIM. Finally, we observed that while proneural GSCs treated with endothelial EVs have inactivated NOTCH pathway, NFkB pathway is activated facilitating the proneural to mesenchymal switch allowing responsiveness to chemotherapy and trigger infiltrative growth pattern in the brain. Our findings suggest that angiocrine interactions impact the nature of cellular 'stemness' in GBM with implications for disease biology and therapy.

Taken together, our study offers a new understanding of the EV mode of angiocrine effects on tumour stem cell hierarchy, which may have both diagnostic and therapeutic significance in GBM.

44 - Skull And Vertebral Abnormalities Observed in Sf3b4+/- Mice Recapitulates Abnormalities Found in Patients with Sf3b4 Heterozygous Mutation

PhD - Senior

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Nager and Rodriguez syndromes are rare disorders caused by haploinsufficiency of SF3B4, a core component of the U2 complex of the splicing machinery. Patients usually have craniofacial as well as limb abnormalities with variable expressivity including small jaw bones, small cheek bones, radial-ulnar defects, and thumb abnormalities. To study the abnormalities caused by haploinsufficiency of Sf3b4, we generated a conditional mutant mouse line using CRISPR/Cas9 and mated it to βactin-Cre transgenic mice on both CD1 and C57 genetic backgrounds, leading to heterozygous deletion of Sf3b4 in these mice. At E17.5, $Sf3b4^{+/-}$ embryos had smaller and flatter skulls and were overall smaller compared to their control litter mates. Vertebral defects were also observed in these embryos. In both backgrounds, 100% of the $Sf3b4^{+/-}$ embryos had cervical abnormalities ranging from partial to complete ectopic rib at C7. Vertebral transformation of the T1 was observed in C57 embryos. Approximately 85% of the CD1 embryos and 100% of the C57 had a missing lumbar vertebra. Abnormalities were also observed in the sacral vertebrae in both backgrounds. Preliminary analysis using qPCR showed a decrease in Hox gene expression in $Sf3b4^{+/-}$ embryos indicating a role for Sf3b4 in regulating the expression of Hox genes. Apart from craniofacial abnormalities, SF3B4 patients also have abnormal vertebral segmentation, rib abnormalities as well as central nervous system anomalies, as found in our $Sf3b4^{+/-}$ mouse model. Thus, our model can be used to uncover the splicing and molecular events regulated by SF3B4 during development of the vertebrae.

45 - Validation of a Costing Algorithm in the Neonatal Intensive Care Unit and Identification of Cost Drivers for Neonates

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Context: Neonatal Intensive Care Units (NICUs) account for over 35% of pediatric in-hospital costs, thus implying that a better understanding of expenditures is a vital step for improving efficiency of care. The Canadian Neonatal Network (CNN) algorithm is the first to provide case-specific costs based on resource usage among infants born <37 weeks but has not yet been validated for other populations in the NICU.

Objective: To validate the CNN costing algorithm in 7 case-mix categories with real-time costs in a tertiary-level NICU and assess the variations in costs across within the NICU.

Methods: A retrospective cohort study of all patients admitted within 24h of birth to a Level 3 medico-surgical NICU 2016-2019. Patient demographics, clinical information and CNN predicted costs were obtained from the CNN database. Real-time costs were obtained from the hospital financial software (CPSS). Costs were adjusted using the Cost of Standard Hospitalization Stay to account for inter-provincial price variations.

Results: Among the 1795 live infants admitted, 167 (9.3%) were <29 weeks gestational age (GA), 193 (11%) were 29-32 weeks GA, 457 (25.5%) were 33-36 weeks GA, 144 (8%) had major congenital anomalies and the rest were term-born (>36 weeks GA). Median costs varied according to each case-mix from $5,563 for term infants admitted for other reasons to $180,145 for infants born <29 weeks GA. Despite high variation in total costs, there were small variation in mean daily costs (range: $1,261-$1,943). Overall, the CNN algorithm strongly correlated with CPSS total costs across all 7 case-mix categories (rho range 0.78-0.98, $p<0.01$).

Conclusion: The CNN algorithm accurately predicts NICU total costs for 7 case-mix groups. Costs per day were varying across tertiles of hospitalization, thus suggesting that reductions in length of stay through optimal discharge strategies would be the most efficient method to reduce NICU costs.

46 - The COVID-19 Immunity Task Force Metadata Catalogue

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Introduction: The COVID-19 Immunity Task Force (CITF) was launched in 2020 to track the spread of the SARS-CoV-2 virus in Canadians, and priority sub-populations. To leverage its research capacities, CITF is developing core sets of harmonized data integrated across studies, complemented by a centralized web-based metadata catalogue documenting SARS-CoV-2 virus studies and variables content. The catalogue provides the Canadian and international research communities with the resource to leverage leading-edge research and optimize the use of Canadian studies' data and biological samples related to the SARS-CoV-2 virus.

Methods: The catalogue was created using the software and methods developed by Maelstrom Research and will include over 65 studies. The studies are documented in collaboration with the study investigators and data managers. Information is gathered to provide detailed descriptions of each study design, populations, data collection events and the variables content at each event of data collection. All variables are classified under domains of information, to facilitate identification of studies collecting information of interest.

Results: There are currently 37 studies described in the catalogue. Together, the catalogued studies recruited over 600,000 participants across Canada, the numbers varying from below 200 to over 300,000 participants per study. Most of the studies are cohorts (N=27), 18 recruited Quebec participants and 3 specifically targeted mother and child populations. All 37 studies collected biosamples (blood, urine, saliva, nasopharyngeal swab), 33 also collected information from questionnaires and 4 gathered physical measurements. To date, 21 studies provided the list of variables collected, and new studies and variables are added each week (https://www.maelstrom-research.org/network/citf).

Conclusions: While still ongoing, development of the catalogue has been successful thus far. It allowed researchers to identify studies of interest to answer emerging research questions on COVID-19, and currently facilitates the exploration of the harmonization potential across studies.

47 - Understanding focal cortical dysplasia pathogenesis using single nucleus RNA sequencing

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

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

We successfully isolated nuclei, captured and amplified a 10X full length cDNA library from one FCD sample. We enriched our gene of interest using a biotin-tagged gene-specific primer and streptavidin beads followed by on-bead amplification with a second gene-specific primer and a nested PCR using a third gene-specific primer. Over 1,000,000 high-quality full-length molecules were sequenced, of which 40% were on-target. We were able to identify the mutation in 8% of the reads. Short-read sequencing of the 10X library is ongoing and will enable determination of which cell-types carry the mutation.