



CHILD & FAMILY RESEARCH INSTITUTE

2015

STUDENT  
POSTER  
DAY

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# POSTER SESSION ONE

BASIC SCIENCE



**MODERATOR:** Shane Fung

**PARTICIPANTS:** Arshia Beigi  
Stephanie Bourne  
Kathy Chan  
Kristy Dever  
Shera Fisk  
Isabel Jankowski  
Kaylee Sohng  
Thyrza May Toledo  
Hsin Chin Tsai  
Katarina Wind



**Arshia Beigi**, Undergraduate Student  
Supervisor(s): Stefan Taubert

**Title:** Food source dependent gene regulation by the Mediator MDT-15

**Authors:** Arshia Beigi, Grace Goh, Stefan Taubert

### Abstract

Diet can affect gene regulation and organismal phenotypes, but the genetic components that allow adaptation to different diets are mostly unknown. For example, feeding the nematode worm *Caenorhabditis elegans*, a powerful genetic model organism, a bacterial diet of *Comamonas aquaticus* (CA) instead of the standard *Escherichia coli* (EC) lab diet causes dramatic changes in gene expression as well as life-history traits including developmental rate, reproduction and lifespan. The metabolic compound in the CA diet responsible for the observed effects is vitamin B12, which in mammals is required for embryonic development. Vitamin B12 functions mainly in the propionyl-CoA breakdown and methionine/SAM cycle pathways. We have recently found that although worms lacking *mdt-15*, a conserved transcriptional co-regulator, show high embryonic lethality on EC, a CA diet completely rescues this phenotype. Therefore, we hypothesized that the same compound (i.e. vitamin B12) is responsible for the observed rescue in *mdt-15* reduction-of-worms (rf) worms, and that the high embryonic lethality seen in *mdt-15*(rf) worms on EC is due to the lack of B12 in the parental diet. To test the first hypothesis, we grew *mdt-15*(rf) worms on B12-supplemented EC diets, and compared embryonic lethality with mutants fed non-supplemented EC. Interestingly, we found that B12 successfully, albeit not completely, restored the hatching success rate of *mdt-15* worms. Next, we performed a diet-switching experiment whereby *mdt-15*(rf) worms were raised on EC or CA diets. We then moved adult worms to the reciprocal food source, allowed them to lay eggs over a short (3-hour) period, and compared embryonic lethality of the progeny. These results confirmed that the rescue is in fact dependent on the presence of B12 in the parental diet. Recently, we have been investigating which pathway B12 works through in *mdt-15* worms, and our preliminary data indicate that it is not through the methionine/SAM pathway as methionine supplementation fails to rescue the phenotype. Further experiments will focus on the alternate pathway of propionyl-CoA breakdown and its role in the observed rescue. Collectively, this work will determine the role of a conserved transcriptional co-regulator as a genetic buffer for developmental events against adverse environmental effects.

**Stephanie Bourne**, Undergraduate Student  
Supervisor(s): William Gibson

**Title:** Determining the genetic cause for congenital cataracts

**Authors:** Stephanie Bourne, Katlin N Townsend, FORGE Canada Consortium, Ordan Lehmann, Siu Li Young, William T Gibson

### Abstract

A cataract is caused by clouding of the lens of the eye and can be seen in one eye (unilateral) or both eyes (bilateral) in late adulthood. Congenital cataracts are present at birth and if left untreated lead to impaired vision or blindness. The prevalence of congenital cataracts is 1-6 per 10,000 births and almost a third of these cases are inherited. The inheritance pattern of congenital cataracts is usually autosomal dominant, but can also be inherited in an autosomal recessive or X-linked manner. We have identified two unrelated families with a two-generation history of bilateral congenital cataracts showing a dominant inherited pattern. Our hypothesis is that there will be a single rare pathogenic variant that caused the development of congenital cataracts in each of these families.

We have performed Whole Exome Sequencing (WES) on all affected individuals as well as the unaffected grandparents in family 1 to identify rare variants that may cause bilateral cataracts. We searched through the exome sequencing data for shared variants in all affected individuals. This list was further narrowed down by identifying variants in genes involved in eye development and that were predicted to be damaging by protein prediction software. We plan on following the same procedure for family 2 once the WES data becomes available.

We have narrowed down the list to 4 top genes in family 1 (LAMA1, FGFBP3, NPHP4, and FOXI1) based on the effect of the variant on protein function, the frequency of the variant in the population, and protein expression in eye tissue. Future directions will involve comparing variants seen in both families to see if there is a variant in the same gene. We will also use a Zebrafish model to knockdown the genes of interest to see if a similar eye phenotype arises.

**Kathy Chan**, Undergraduate Student  
Supervisor(s): Alexander Beristain

**Title:** Effects of obesity associated inflammation on the maternal-fetal interface in early pregnancy

**Authors:** Kathy Chan, Sofie Perdu, Mahroo Aghababaei, Barbara Castellana, Alexander Beristain

### Abstract

Introduction: Obesity is a rising cause of obstetrical and perinatal morbidity in Canada with over 20% of women of childbearing age defined as being obese. During pregnancy, obese women are three times more likely to develop major complications. Obesity is linked to a higher risk of preterm birth, which is responsible for ~75% of the 4 million neonatal deaths annually worldwide. The increased risk in developing these conditions may be related to obesity-linked changes in immune cells. Immune cell factors directly affect embryo implantation and establishment of the maternal-fetal-interface. However, the mechanism(s) through which obesity-linked inflammation affects pregnancy outcomes are currently unknown. Uterine natural killer (NK) cells comprise 70% of leukocytes within the pregnant uterus. Unlike conventional splenic NKs, uterine NKs are not cytotoxic, but instead produce pro-angiogenic factors, proteases and cytokines important in arterial remodeling. Recently, our lab has shown maternal obesity results in decrease proportions of uterine NKs. This work aims to confirm if maternal obesity leads to absolute decreases in uterine NKs and sets out to examine how spatial localization of NKs is affected.

Methods: Uterine tissue specimens from consenting women undergoing elective pregnancy terminations between 10 and 14 weeks gestation (control BMI = 20-24.9 kg/m<sup>2</sup>, N=7; obese BMI =  $\geq$  30 kg/m<sup>2</sup>, N=11), were examined microscopically. NK and arterial smooth muscle cells were immuno-localized using markers for NKs (CD56) and smooth muscle (smooth muscle actin). Absolute quantification of NKs within tissues was performed using Zen2 imaging software.

Results: In control uterine tissues, NKs were identified throughout the decidua, where dense NK aggregates proximal to arteries were routinely observed. In obese samples, NK cells were also frequently observed, however NK cell aggregates near blood vessels were less frequent.

Conclusion: This work anticipates showing that maternal obesity in early pregnancy associates with a decrease in uterine NK cells. These changes are possibly accompanied by alterations in NK cell activation/aggregation in proximity to uterine arterials. Together, these findings provide novel insight into cellular events impacting healthy establishment of pregnancy in obese women.

**Kristy Dever**, Undergraduate Student  
Supervisor(s): Michael Kobor & Maria Aristizabal

Title: A broader role for Fcp1 in transcriptional regulation

Authors: Kristy Dever, Maria Aristizabal, Michael Kobor

### Abstract

Fcp1 is a phosphatase known to play a regulatory role in transcription elongation and termination by dephosphorylating the C-terminal domain (CTD) of RNA Polymerase II (RNAPII). Despite the functional overlap, FCP1 mutants and RNAPII mutants display different gene expression and genetic interaction profiles, indicating that Fcp1 is functioning in a capacity other than de-phosphorylating the CTD of RNA Polymerase II. In this project, we aimed to expand the role of Fcp1 by identifying additional substrates. Using the gene expression profiles, we identified two putative Fcp1 substrates, the gene-specific transcription factors Sok2 and Skn7, both of which were previously shown to be phosphorylated proteins and whose target genes are particularly sensitive to mutating FCP1. Thus, we hypothesize that by regulating their phosphorylation status, Fcp1 regulates Sok2 and Skn7 function and thus plays additional roles in transcription initiation. Consistent with this hypothesis we observed that Sok2 and Skn7 protein levels were decreased in the fcp1 mutant compared to wild type and through RT-qPCR analysis we determined that these effects were not a result of decreased Sok2 and Skn7 mRNA levels but rather post-transcriptional effects of Fcp1 on Skn7 and Sok2. Further supporting this model, we observed that Skn7 and Sok2 protein stability were decreased in the fcp1 mutant compared to wild type. Future work will aim to further solidify the role of Fcp1 in regulating these transcription factors, by identifying the target phosphorylation sites using in vitro and in vivo systems.



**Shera Fisk**, Undergraduate Student  
Supervisor(s): Laura Sly

**Title:** The role of MALT1 in osteoclast differentiation and activity

**Authors:** Shera Fisk, Mahdis Monajemi, Susan Menzies, Laura Sly

### Abstract

The CARMA1-BCL10-MALT1 (CBM) complex activates Nuclear Factor kappa B (NFκB), which transcriptionally regulates lymphocyte activation and proliferation. Recent studies have found that this pathway is critical in immune-mediated diseases, like inflammatory bowel disease, and cancer. Current research is being done to investigate a homozygous missense mutation in the MALT1 gene, which blocks its normal paracaspase activity and prevents NFκB activation. This research began in response to a patient, who suffers from the effects of nonfunctional MALT1 protein. The phenotype of this disease is widespread and includes severe gastrointestinal inflammation as well as osteoporosis. Investigations of this signalling pathway may be important for patients with defects in the CBM complex as well as to patients receiving MALT1 inhibitory cancer treatments. Our laboratory is examining the role of MALT1 deficiency in macrophage-mediated inflammation, as well as osteoclast proliferation and activity.

The objective of my study is to develop techniques for studying the osteoporosis seen in the MALT1 deficient patient. Osteoporosis presents as a loss of bone density, resulting in an increased risk of fracturing. The regulation of bone density is performed by the balance between osteoblasts, cells that create bone, and osteoclasts, cells that degrade bone. In order to examine our patient's reduced bone density, osteoclast proliferation and activity, as well as overall development will be compared between wild type and MALT1 deficient C57BL/6 mice at 4, 6, 8, and 12 weeks of age. Osteoclast numbers will be determined in vitro by culturing them on slides, and in vivo by bone sectioning and staining. Osteoclast activity will be measured through the use of dentine plate degradation, which simulates in vivo bone resorption. Lastly, overall skeletal development will be assessed in mice by measuring the weight and length of the mice and their femura at each age. These studies will be the first to investigate the direct effect of MALT1 and MALT1 deficiency in osteoclastogenesis and function.

**Isabel Jankowski**, Undergraduate Student  
Supervisor(s): Tobias Kollmann

**Title:** Age-dependent differences in STING-mediated Type 1 Interferon Production

**Authors:** Isabel Jankowski, Zach Liang, Mathieu Garand, Byron Brook, Tobias Kollmann

### Abstract

Neonates and infants have been known to suffer greater severity of infection from pathogenic agents, including *Mycobacterium tuberculosis*, *Listeria monocytogenes*, and Influenza among the more well-known. Increasing evidence suggests that Type 1 Interferons (IFN), a class of cytokines generally thought to play a protective role during intracellular infections, may be involved in the observed increased disease severity caused by some of these pathogens. A survey of various cytosolic pattern recognition receptors (cPRRs) previously conducted in the lab revealed higher levels of IFN- $\alpha$  (a Type 1 IFN) in cord blood compared to their adult counterparts when stimulated with ligands activating the Stimulator of Interferon Genes (STING) protein, one of several cPRRs. This finding, coupled with the possible disease-enhancing role of Type 1 IFN and the involvement of STING during relevant infections, have led us to believe that the greater burden of infection that neonates experience from certain intracellular pathogens is due to differences within the STING signalling cascade.

In order to dissect the STING-mediated pathway, Enzyme-Linked Immunosorbent Assay (ELISA) was used to measure adult and neonatal levels of the IFN- $\alpha$  response to different STING ligands, in both whole blood (WB) and peripheral or cord blood mononuclear cells (PBMC or CBMC). Consistent with previous experiments, STING ligands induced a much higher IFN- $\alpha$  response in cord compared to adult WB. Interestingly, the trends were reversed in PBMC/CBMC, with a higher response in adults, suggesting the possible involvement of extracellular immune factors. Repeating the ELISA with different sources of plasma revealed that the elements responsible are likely not contained within plasma.

Thus far, our findings suggest that there are in fact differences in the STING signalling cascade between adults and neonates. Presently, we are working towards characterizing other parts of the pathway, such as differences in protein levels, cell composition, and cell-cell interactions. Progress in this research will be a step towards better health outcomes for our very young.

**Kaylee Sohng**, Undergraduate Student  
Supervisor(s): Soren Gantt

**Title:** Genetic variability of gp350 in Ugandan pediatric Epstein-Barr virus infections

**Authors:** Kaylee Sohng, Wendy Bernhard, Dong Jun Zheng, Soren Gantt

### Abstract

Epstein-Barr virus (EBV), a member of the family of human herpesviruses, is transmitted through saliva and invades B cells in lymphoid tissue. It infects 95% of the world population and, together with co-factors like malaria, can cause Burkitt's lymphoma, the leading cause of childhood cancer death in Africa. The membrane surface glycoprotein gp350 (encoded by gene BLLF1) plays a major role in virion attachment by binding to the CR2 receptor of target B lymphocytes. Previous work has identified substantial variation in the BLLF1 sequence with an increased ratio of non-synonymous to synonymous mutations (NS:S), suggesting that gp350 may undergo selective pressure towards antigenic drift.

We currently possess the largest existing longitudinal cohort of EBV samples, made up of weekly saliva and blood samples collected over 57 weeks from 113 Ugandan subjects. These include samples collected from infants, mothers, and any siblings in the same home. DNA was extracted from matched blood and saliva samples using the QIAGEN DNeasy Blood & Tissue Kit, target enrichment was performed by Q5 PCR amplification of BLLF1, and Sanger sequencing was performed.

Upon receiving the resulting sequences, multiple sequence alignment will be performed using ClustalW2 to determine a consensus sequence, and variants will be confirmed by inspection of the sequencing traces. We will then construct a phylogenetic tree of gp350 variation using the PhyML maximum likelihood model. We expect to observe increased NS:S ratio, compartmentalization of variants between blood and saliva, and predominance of viral transmission between the mother and infant rather than from siblings. We also expect to see correlations between observed viral lineage and behavioral survey data collected from the mothers. We may also perform follow-up sequencing of interesting subjects using samples collected at different time points to observe the dynamics of viral evolution.

By population-based sequencing of gp350, we aim to characterize the genetic diversity of this key glycoprotein in EBV. We expect that this work will improve understanding of the molecular basis of EBV compartmentalization, transmission, and antigenic drift.

**Thyrza May Toledo**, Undergraduate Student  
Supervisor(s): Suzanne Vercauteren

**Title:** Dried blood spots for long term storage of analytes for research purposes

**Authors:** Thyrza May Toledo, Tamsin Tarling, Katelin Townsend, Nidhi Arora, John Bhullar, Suzanne Vercauteren

### Abstract

Unlike liquid blood, dried blood spots (DBS) can be stored and transported at ambient temperature thereby reducing the need for expensive storing and transportation systems. We compared the quantity and purity of DNA extracted from blood collected in Ethylenediaminetetraacetic acid (EDTA), blood spots made from EDTA collected blood and blood spots made from whole blood. To determine the effect of temperature and light on the quality and quantity of DNA, blood spots were stored inside paper and light protected envelopes at various temperatures.

Whole blood DBS were prepared by spotting blood drops from a syringe onto Whatman 903 cards while EDTA DBS were prepared by spotting 70 $\mu$ L of the EDTA blood sample onto DBS cards. The cards were air dried at room temperature for 3 hours, placed inside paper or light protected envelopes and stored at room temperature, 4 $^{\circ}$ C, -20 $^{\circ}$ C or -80 $^{\circ}$ C for 1, 3, 6 and 12 months. DNA extracted using the QIAamp DNA Micro Kit was quantified using the NanoDrop. DNA purity was determined using the A260:A280 and A260:A230 ratios and DNA quality was assessed by agarose gel electrophoresis (AGE).

Our study found that the EDTA DBS and whole blood DBS gave comparable DNA yield (0.32 $\pm$ 0.01 $\mu$ g versus 0.38 $\pm$ 0.02 $\mu$ g), suggesting that the DNA stability is similar whether the blood spotted on the DBS cards is collected in an anti-coagulant or not. Also, the DBS stored inside paper and light protected envelopes had a mean DNA yield of 0.34 $\pm$ 0.11 $\mu$ g and 0.34 $\pm$ 0.07 $\mu$ g respectively, suggesting that in the short term, light does not affect the DNA yield. Unfortunately, the one month and three months results were inconclusive in terms of which storage temperature was optimal for the blood spots. Therefore, more replicates should be performed. In terms of DNA purity, the AGE images showed no RNA contamination but the A260:A230 ratios suggest salt or alcohol contamination. Thus, in the future, further DNA purification steps should be performed.

We conclude that anti-coagulant, like EDTA does not affect the quantity or quality of extracted DNA from blood spots. The optimal storage temperature of blood spots for future DNA extraction is yet to be determined.

**Hsin Chin Tsai**, Undergraduate Student  
Supervisor(s): Bruce Vallance & Shauna Crowley

**Title:** Exploring the role of epithelial inflammasome in restricting Salmonella enteric serovar Typhimurium infection

**Authors:** Hsin Chin Tsai, Shauna M Crowley, Bruce A Vallance

### Abstract

**Introduction:** Salmonella enteric serovar Typhimurium is an enteric bacterial pathogen that causes gastroenteritis in millions of Canadians each year through contaminated food products. Understanding the mechanism by which intestinal epithelial cells (IECs) protect the host from enteric pathogens is paramount to our ability to prevent and treat food-borne illness. Our group recently reported that intestinal colonization by S. Typhimurium was restricted through an IEC-intrinsic defensive mechanism. We also observed in vivo that the IECs actively engaged in immune defense through the activation of an IEC-specific inflammasome, which triggered epithelial extrusion of infected cell into the gut lumen. However in order to further characterize the murine epithelial inflammasome, development of an epithelial cell model is required.

**Methods:** CMT93 were subjected to a gentamicin protection assay where cells were infected with S. Typhimurium for 0, 30min, 1h or 8h before exposure to gentamicin. Cell lysates were plated and quantified via serial dilution. We also utilized murine organoids, which are three-dimensional "epithelial miniature guts," formed using a specialized ex vivo culturing technique from C57BL/6 intestinal crypts. S. Typhimurium was injected into the organoid lumen via a micro-injector to mimic an apical infection for 4h or 16h. The extent of S. Typhimurium infection and inflammasome activation was assessed by both immunostaining and Western blot.

**Results:** Utilizing an MOI of ~35 S. Typhimurium: 1 CMT93 cell, we observed an increase in the percent bacterial invasion of CMT93 over time. Within the first 30 min of infection, there was 0.382% invasion, which drastically increased to 150% invasion at 8h post infection. Immunofluorescence images of the CMT93 monolayers also illustrated this trend with ~2 S. Typhimurium per a single CMT93 cell at 30 min and ~20 at 8h. Interestingly, immunofluorescence imaging revealed a subpopulation of CMT93 cells which were hyper-infected at 8h, which is consistent with in vivo data previously published by our group.

**Conclusion:** These findings established CMT93 cells and intestinal organoids as two models for the study of the epithelial inflammasome. S. Typhimurium infection of both cell types mimicked in vivo phenotypes and will be implemented to further characterize the role of the IEC inflammasome in restricting enteric infection.

**Katarina Wind**, Undergraduate Student  
Supervisor(s): Bruce Verchere

**Title:** Exploiting  $\beta$ -cell metabolism to prevent alloimmune rejection of islet grafts

**Authors:** Katarina Wind, Azadeh Hosseini-Tabatabaei, Derek Dai, Bruce Verchere

### Abstract

Background and Hypothesis: Transplantation of insulin-producing beta cells is a potential cure for type 1 diabetes, however immune rejection remains a major hurdle. Beta cells produce negligible amounts of lactate, a molecule that cancer cells produce as a local immunosuppressant to evade immune attack. We hypothesize that production and secretion of lactate by transplanted beta cells will prolong islet allograft function and survival in a mouse model.

Methods: Adeno-associated virus 8 (AAV8) expressing lactate dehydrogenase A (LDHA) and monocarboxylate transporter 1 (MCT1) driven by the rat insulin promoter was created previously to induce production and release of lactate from beta cells. This virus, or a mock vector control, was introduced via intra-pancreatic duct (ID) injection into BALB/c mice. Two weeks following ID injection, untreated or viral-transfected islets were isolated and transplanted into diabetic C57Bl/6 mice. Recipient mice were previously rendered diabetic by a single intraperitoneal (IP) injection of streptozotocin a few days before transplantation. Additionally, some virally transduced BALB/c islets were isolated for glucose-stimulated insulin secretion (GSIS) and RT-qPCR analyses. Recipient mice were monitored for graft function and survival. Upon graft rejection, mice were euthanized and their tissues were harvested for histological analysis. In a separate experiment, isolated CD3+CD4+ and CD3+CD8+ splenocytes were treated with various concentrations of lactate in vitro and cell viability was assessed using FACs analysis.

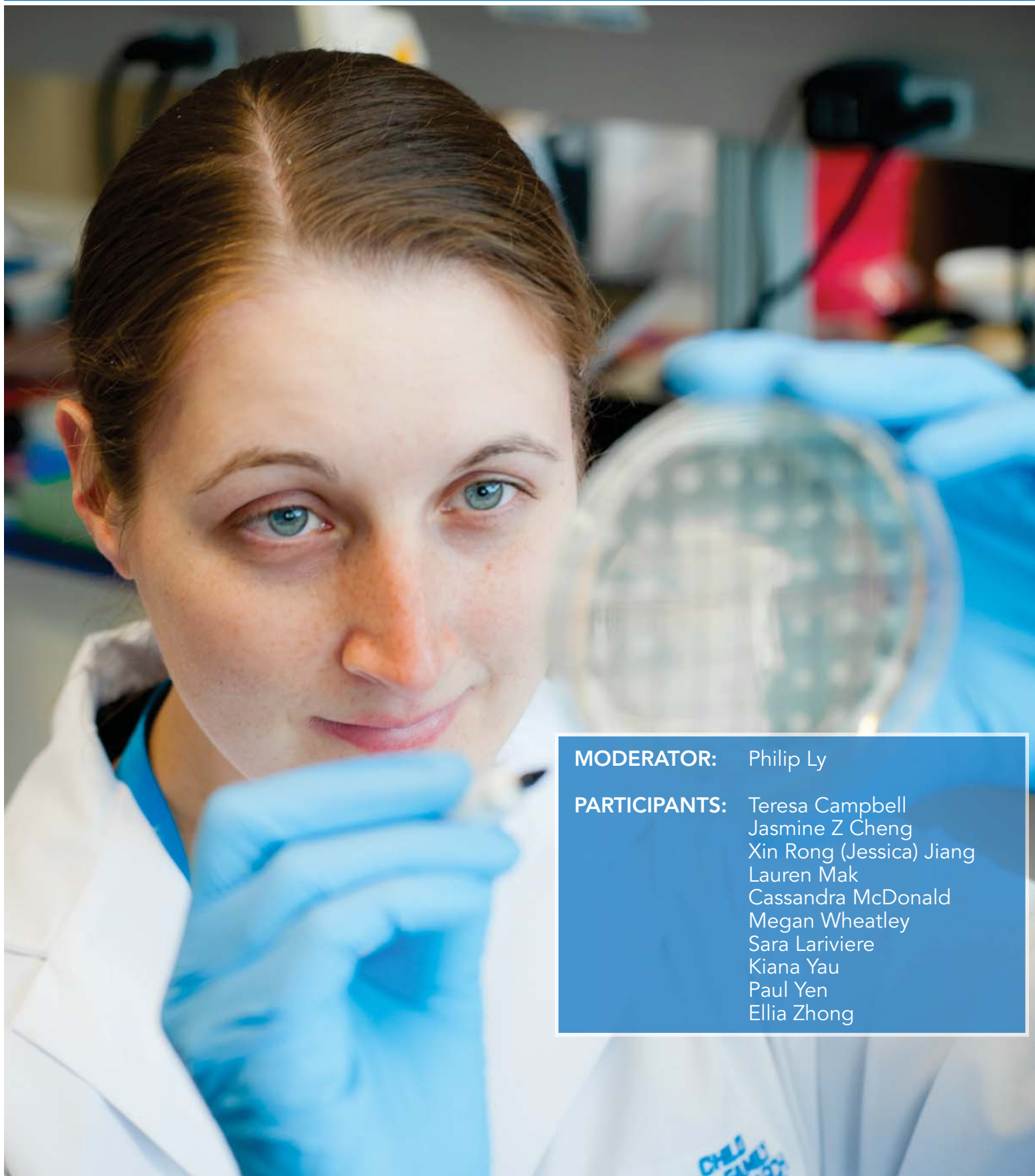
Results: RT-qPCR analysis showed increased expression of LDHA and MCT1 in AAV8-LDHA-MCT1 transfected islets. Additionally, islets transfected with AAV8-LDHA-MCT1 released significantly more lactate than mock vector controls in response to glucose stimulation. Furthermore, lactate reduced the viability of CD4+ and CD8+ T cells in vitro. Preliminary results from the transplant experiments suggest that local lactate production in LDHA/MCT-1 expressing islets prolongs allograft survival and function in vivo.

Conclusions and Significance: Our preliminary results show that lactate may protect transplanted islets from alloimmune rejection, without disrupting the functionality of these islets. Therefore, inducing lactate production may be a novel way to improve the outcome of islet transplantation in patients with type 1 diabetes.



# POSTER SESSION TWO

BASIC SCIENCE



**MODERATOR:** Philip Ly

**PARTICIPANTS:** Teresa Campbell  
Jasmine Z Cheng  
Xin Rong (Jessica) Jiang  
Lauren Mak  
Cassandra McDonald  
Megan Wheatley  
Sara Lariviere  
Kiana Yau  
Paul Yen  
Ellia Zhong

**Teresa Campbell**, Undergraduate Student  
Supervisor(s): Bruce Vallance

**Title:** Primary epithelial cell lines derived from 3D organoid structures, as a model for *Campylobacter jejuni* infection

**Authors:** Teresa Campbell, Martin Stahl, Bruce A Vallance

### Abstract

Immortalized cell lines are commonly used in the laboratory as a tool to study the physiology of the intestinal epithelium. Despite the useful nature of these in vitro models, caveats such as the lack of cell differentiation and genetic diversity, limit the use of cell lines in intestinal research. Recent advances in the understanding of intestinal stem cell physiology, has lead to the development of a new model system termed the intestinal organoid. Intestinal organoids are 3D organ structures grown ex vivo from pluripotent stem cells. Organoids offer a clean model system that imitate epithelial structure, physiology, and cell diversity; however present their own limitations in regards to ease of use and accessibility. Based on this new model system, we hypothesize that it is possible to use 3D organoid structures to create 2D primary epithelial cell lines.

Using novel culturing techniques, progenitor epithelial cells were dissociated from organoid structures and seeded onto a Gel-trex coated cover slip, mimicking the structure of the intestinal basement membrane. Cells were allowed to proliferate over time, resulting in a confluent monolayer of primary epithelial cells. Monolayers were further investigated as an infection model for the common enteric pathogen *Campylobacter jejuni*. Infection of the monolayer with this pathogen displayed both adherence and invasion of the cell line, suggesting this model could be used to further investigate the mechanism of *Campylobacter jejuni* pathogenesis. In conclusion, our research has shown it is possible to create 2D primary epithelial cell lines from organoid structures, and offers an exciting model system for future studies of *Campylobacter jejuni* pathogenesis in the intestinal epithelium.

**Jasmine Z Cheng**, Undergraduate Student  
Supervisor(s): Stuart Turvey

**Title:** The impact of the intestinal microbiota on human immune development and atopic disease

**Authors:** Jasmine Z Cheng, Leah T Stiemsma, Marie-Claire Arrieta, Pedro A Dimitriu, Lisa Thorson, Sophie Yurist-Doutsch, Rollin Brandt, Diana L Lefebvre, Padmaja Subbarao, Piush Mandhane, Allan Becker, Malcolm R Sears, Tobias Kollmann, Soren Gantt, William W Mohn

### Abstract

Background: Asthma is the most prevalent childhood disease affecting over 300 million people worldwide. Recently our research group associated features of the early life gut microbiota in children (at 3-months and 1-year of age) with risk of active asthma at school age (determined by the Asthma Predictive Index). These features included underrepresentation of four bacterial genera and a decreased production of microbial derived metabolites. We hypothesize that a dysbiotic early life gut microbiota is associated with asthma pathogenesis. This study seeks to further identify differences in various bacterial taxa that may be associated with this asthmatic phenotype.

Methods: Children enrolled in the Canadian Healthy Infant Longitudinal Development (CHILD) study were classified as asthmatics if at 3 years of age they were clinically diagnosed with asthma and/or taking asthma medication, or if between 4 and 5 years of age they were taking asthma medications. Bacterial 16S rDNA from 3-month and 1-year stool samples from these children was extracted, amplified, and subjected to high throughput Illumina sequencing. Specific bacterial genera and species were quantified by quantitative PCR (qPCR) from asthmatic and control children (who have no history of asthma symptoms).

Results: 16S sequence analysis of our sample cohort identified differentially abundant bacterial populations between asthmatics and controls in stool collected at 3-months and 1-year of age. Additionally, qPCR identified significant shifts in the abundance of *Clostridium neonatale* and *Lachnospira* spp. between asthmatics and controls at 3-months and 1-year of age.

Future Directions: Our group aims to analyze the clinical significance of these results in terms of their relevance to asthma pathogenesis potentially using short chain fatty acid and/or metabolomics analyses.

**Xin Rong (Jessica) Jiang**, Undergraduate Student  
Supervisor(s): Angela Devlin

**Title:** The effect of maternal folate and B12 imbalance on offspring skeletal muscle Ppargc-1a gene expression

**Authors:** Xin Rong (Jessica) Jiang, Daven Tai, Angela Devlin

### Abstract

Background: Folate is a coenzyme in DNA synthesis and also acts a methyl group donor in DNA methylation. Since the start of folic acid fortification program in Canada, there has been a 46% decrease in neural tube defect rate. Folate deficiency in Canada is now rare, however 5% of the population is deficient in vitamin B12, which is metabolically linked to folate. Population studies report that an imbalance of maternal folate and vitamin B12 status during pregnancy programs adiposity and insulin resistance in children.

The mechanism behind folate/B12 imbalance and offspring metabolic health remains unclear. Peroxisome proliferator-activated receptor  $\alpha$  coactivator 1alpha (Ppargc-1a), is a transcriptional coactivator for the muscle insulin sensitive glucose transporter, GLUT4. Studies have reported lower Ppargc-1a expression in skeletal muscle from subjects with type II diabetes, and a negative association between Ppargc-1a expression and fasting insulin concentrations.

Devlin lab has developed a mouse model in which adult female C57BL/6 mice were fed a control diet or a folic acid-supplemented diet in the absence or presence of vitamin B12 (HFA-B12 and HFA+B12, respectively) from six weeks before pregnancy until weaning. The offspring were weaned on to control or western diet (45% energy from fat).

Objective: To quantify Ppargc-1a mRNA in skeletal muscle of adult offspring from dams fed diets differing in folate and vitamin B12 during pregnancy.

Methods: Skeletal muscle tissues were harvested from female offspring (n=5-6/group). RNA was extracted using the Qiagen RNeasy Prep Kit. RNA concentration was determined by a NanoDrop spectrophotometer. RNA was converted to cDNA using the High Capacity cDNA Reverse Transcription Kit. Ppargc-1a mRNA was quantified by Real-Time PCR using the ddCt method of quantification and 18s ribosomal RNA as an endogenous control.

Future experiments: To further understand the mechanism differences underlying varying glucose tolerance levels of offspring from different dam diet group, Ppargc-1a promoter methylation will be measured. Additionally, since Ppargc-1a is a coactivator for glucose transporter GLUT4, the expression level of GLUT4 will also be measured.

**Lauren Mak**, Undergraduate Student  
Supervisor(s): Kelly Brown

**Title:** Classification biomarkers for pediatric chronic primary vasculitis

**Authors:** L Mak, E Gill, R Falsafi, S Hughes, REW Hancock, KL Brown, DA Cabral,  
PedVas Co-Investigators

### Abstract

Chronic primary vasculitis (CPV) in children is a group of rare diseases characterized by inflammation of blood vessels in vital organs of the body. The etiology and mechanism of the diseases are currently unknown, and as a result the different subtypes of CPV are roughly classified based on the size of affected vessels and clinical presentation. This classification system is imperfect, failing to classify up to two-thirds of patients and falling short of informing treatment even for patients with an identified subtype. There is evidence to suggest that subtype-specific care guidelines would improve patient outcomes, but developing them is only possible if subtypes can be clearly defined. A group of rheumatologists and research scientists based in Canada have been leading a multi-center longitudinal study on childhood CPV called PedVas. The overarching goal is to improve outcomes for children with CPV in part through the generation and integration of biological evidence and clinical observation into current CPV classification criteria. One of PedVas' major objectives is to differentiate granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA), two CPV subtypes that are difficult to distinguish on clinical indications alone. Though differences in clinical phenotype have been identified, the underlying gene expression distinctions have not yet been studied. Whole blood RNA was isolated from patients with GPA and MPA, and followed by RNA sequencing and advanced bioinformatics analysis. Preliminary results show differentiating patterns of gene expression in patients with GPA and MPA, and future steps involve qPCR for technical confirmation of RNAseq indications and determining the pattern of expression in other CPV subtypes. Finding reliable biomarkers to differentiate between GPA and MPA will improve classification specificity, and allow treatment plans to be tailored to patients according to the subtype.

**Cassandra McDonald**, Undergraduate Student  
Supervisor(s): Brad Hoffman

**Title:** The core trithorax protein Wdr5 is essential for pancreas progenitor differentiation

**Authors:** Cassandra McDonald, Stephanie Campbell, Bradford Hoffman

### Abstract

Type 1 Diabetes (T1D) is a metabolic disorder characterized by the autoimmune destruction of pancreatic  $\beta$ -cells. The most common treatment for T1D is lifelong dependence on insulin injections, so there is great interest in finding an insulin-independent, long-term cure for T1D patients. Currently, the most promising avenue is through transplantation of islets from deceased donors; however, the demand far exceeds the availability of donor islets. To meet the need for large numbers of functional  $\beta$ -cells, growing research is aimed at directing stem cell differentiation towards a functional  $\beta$ -cell fate in vitro; however, this has not yet been entirely successful. We believe that there are underlying epigenetic mechanisms that prevent complete pancreas progenitor differentiation. Previous studies in our lab have shown that transcription factors essential for pancreas development require specific chromatin marks in order to be expressed. In particular, our research implicates the function of the chromatin-remodeling Trithorax Group (TrxG) complex that is known to activate and maintain gene expression in certain developmental pathways via methylation of histone H3. Thus, we hypothesize that the TrxG complex is essential for pancreas progenitor differentiation.

To test our hypothesis, we utilized an in vitro model of pancreas development with mouse pancreas progenitor spheroids that differentiate in 3D Matrigel culture into all three pancreas lineages. To determine the role of the TrxG complex in sphere differentiation, we developed an shRNA-mediated knock-down lentivirus targeting the essential TrxG subunit Wdr5. Mouse pancreas progenitors are dispersed and transduced with shWdr5 or control shScramble lentivirus, and cultured for 7 days with specific growth factors to induce proliferation and differentiation. On certain days, we count, image, and measure the diameter of the spheroids, then collect them for gene expression analysis. By day 7, shWdr5 spheroids are significantly smaller and there are fewer compared to shScramble. This suggests that shWdr5 spheroids either have impaired proliferation or increased apoptosis compared with controls. Additionally, shWdr5 spheroids have significantly decreased expression of the endocrine cell regulator, Ngn3, as well as islet transcripts Ins1 and Gcg. This indicates that shWdr5 spheroids have impaired endocrine lineage differentiation. Taken together, these results support our hypothesis that the TrxG complex is essential for pancreas progenitor differentiation.



**Megan Wheatley**, Undergraduate Student  
Supervisor(s): Gregor Reid

**Title:** The effects of early infections on acute lymphoblastic leukemia

**Authors:** Megan Wheatley, Mario Fidanza, Arnawaz Bashir, Gregor Reid

### Abstract

Acute Lymphoblastic Leukemia (ALL) is the most common malignancy in children. Recent epidemiological studies have shown that mild, early-life infections can have a protective effect against ALL development. However, it is unknown how and why these early infections have such an effect. Our hypothesis is that these early-life infections affect pre-leukemic cells that arise long before overt disease. Our goal was to determine how early-life infections impact pre-leukemia progression and to define the optimal treatment window for interventions that could potentially be used in the future to prevent leukemia progression.

To achieve this, we injected leukemia-prone Emu-Ret transgenic mice with attenuated listeria on day 6 and day 34 of age, and followed them to time of disease. We found a significant survival advantage of a median of 43 days in the mice injected with listeria compared to the untreated mice. To determine the optimal treatment window for the injection, we injected groups of mice at one time-point each: 6, 14, 21, and 34 days. We obtained the spleens of these mice at day 42 and quantified the pre-leukemic cell burden using flow cytometry. We found a significant reduction in the pre-leukemic burden in the mice injected at 6 days of age, a slight decrease in the mice injected at 14 days of age, and little to no effect in the mice injected at 21 and 34 days of age.

After analyzing our data, we have concluded that listeria infection early in life significantly decreases the pre-leukemic cell burden in leukemia-prone mice, leading to a delayed onset of ALL. The early time window for the treatment may suggest that an aspect of the early immune environment in the young mice could be optimizing this protective effect. Our experiment is a starting point for understanding the protective effect of early infections on ALL. One of the next steps is to begin to understand the mechanism of this protective effect, in hopes that it can be therapeutically applied to remission patients to protect against clonal outgrowth

**Sara Lariviere**, Undergraduate Student  
Supervisor(s): Todd Woodward

Title: Inner speech processing dichotomy

Authors: Sara Lariviere, Todd S Woodward

### Abstract

Auditory-verbal hallucinations (AVH) in schizophrenia are thought to result from a disconnection in regions within the language network. In the present study, we reanalyzed data from a task that required inner speech processing using Constrained Principal Component Analysis for functional magnetic resonance imaging (fMRI-CPCA). This method enables derivation of distinct, simultaneously active, functional brain networks that vary as a function of task-timing. Healthy control subjects (n = 16) and schizophrenia patients with (n = 19) and without AVH (n = 14) performed an fMRI task in which they were shown two-syllable Dutch words and had to evaluate the position of the metrical stress (phonological condition) as well as the valence of the word (semantic condition). The whole-brain functional analysis revealed that two brain networks are involved in making phonological and semantic judgements; an attentional network of coordinated activity and a reciprocal default mode deactivation. Schizophrenia patients with AVH exhibit significant hyperactivity in the default mode network relative to schizophrenia patients without AVH and healthy control subjects. Altogether, these findings suggest that schizophrenia patients, irrespective of hallucination status, have delayed cognitive processes related to making phonological and semantic judgements, which may be reflective of a disconnection between frontal and temporal language processing. Accordingly, this frontotemporal disconnection may originate from reduced activity decreases in regions within the default mode network.

**Kiana Yau**, Undergraduate Student  
Supervisor(s): Bruce Verchere

**Title:** Islet amyloid polypeptide (IAPP) aggregates induce islet inflammation through activation of toll-like receptor (TLR2) signalling.

**Authors:** Kiana Yau, Heather C Denroche, C Bruce Verchere

### Abstract

**Background:** Islet amyloid formed by insoluble aggregates of the beta-cell derived hormone, IAPP, is thought to contribute to beta-cell dysfunction in type 2 diabetes, however, the mechanism is unclear. We previously found that in mice expressing human IAPP (rodent IAPP cannot form aggregates), IAPP aggregates recruit macrophages to pancreatic islets and induce secretion of pro-inflammatory cytokines that impair beta-cell function and contribute to impaired glucose metabolism. Preliminary in vitro data suggest that this process is dependent on activation of TLR2 signalling in islet macrophages.

**Hypothesis:** We hypothesized that TLR2 plays a role in IAPP-induced islet inflammation and beta-cell dysfunction in vivo.

**Methods:** To test this, we crossed hIAPP transgenic mice (which develop robust islet amyloid, islet inflammation, and a type 2 diabetes-like phenotype, on a high fat diet) with global Tlr2 knockout (Tlr2<sup>-/-</sup>) mice, to generate hIAPP transgenic mice with (Tlr2<sup>+/+</sup>; hIAPP<sup>Tg/0</sup>) and without (Tlr2<sup>-/-</sup>; hIAPP<sup>Tg/0</sup>) functional TLR2, in addition to non-hIAPP transgenic Tlr2<sup>+/+</sup> and Tlr2<sup>-/-</sup> littermate controls. The mice were put on high fat diet (45% kcal) for 20 weeks, during which 4-hour fasted and non-fasted body weight and blood glucose levels were monitored weekly. Glucose tolerance tests were performed prior to, during and at the end of 20 weeks of high fat diet. In addition, insulin tolerance tests were performed at the end of 20 weeks of high fat diet to assess insulin sensitivity.

**Results:** On high fat diet, body weights of both the hIAPP transgenic mice and non-transgenic mice increased, but there was no significant difference between the two groups. As expected, the blood glucose levels of hIAPP transgenic mice were significantly greater than non-transgenic mice ( $p < 0.05$ ), however no significant difference was found between Tlr2<sup>+/+</sup>; hIAPP<sup>Tg/0</sup> and Tlr2<sup>-/-</sup>; hIAPP<sup>Tg/0</sup> mice. In addition, hIAPP transgenic mice displayed glucose intolerance and insulin resistance compared to hIAPP non-transgenic mice, but there was no significant difference in glucose excursion and insulin sensitivity between Tlr2<sup>+/+</sup>; hIAPP<sup>Tg/0</sup> and Tlr2<sup>-/-</sup>; hIAPP<sup>Tg/0</sup> mice.

**Conclusions:** Our data reveal that global TLR2 deficiency does not protect from IAPP-induced impairments in glucose metabolism in hIAPP transgenic mice, suggesting that IAPP-induced islet inflammation may not require TLR2 signalling.

**Paul Yen**, Undergraduate Student  
Supervisor(s): Bruce Verchere

**Title:** Accumulation of islet amyloid polypeptide (IAPP) precursors induces early islet transplant failure

**Authors:** Paul P H Yen, Jaques A Courtade, Derek L Dai, Galina Soukhatcheva, Paul C Orban, C Bruce Verchere

### Abstract

**Background:** Transplantation of insulin-producing beta-cells is a potential cure for type 1 diabetes, although the majority of islet transplants fail within five years. Previous studies demonstrate that accumulation of aggregates of islet amyloid polypeptide (IAPP is normally made by beta-cells) promotes early graft failure. Production of IAPP from proIAPP in beta-cells requires the prohormone convertases PC1/3 and PC2. When islets from mice lacking PC2 are transplanted into diabetic recipient mice, the grafts fail rapidly, but the mechanism behind this process is not understood.

**Aim:** We aim to determine whether IAPP precursors mediate islet graft failure via inflammatory or ER-stress pathways, based on the ability of mature IAPP to misfold and promote inflammation.

**Methods:** To address this hypothesis, islets from wild-type C57B6 mice were treated with virus that overexpressed rodent proIAPP (which does not aggregate), human proIAPP or human proIAPP(KHK) (a protein variant that cannot be cleaved by PC2). After ten days in culture, RNA was extracted and we examined transcript abundance of processing enzymes/chaperones (Pcsk1, Pcsk1n, Pcsk2, Sgna1, Cpe, Pam), inflammation markers (cd11b, Il-1 $\beta$ , Tlr2, Nlrp3) and ER stress mediators (Hspa5, Atf4, Xbp1, Ddit3). In addition, islets from mice expressing human proIAPP with or without PC2 expression were transplanted into diabetic NOD.SCID recipients, which were sacrificed at six weeks post-transplant for gene expression analysis.

**Results:** In isolated islets overexpressing human proIAPP, there were trends toward general upregulation of transcripts involved in maturation of proIAPP to IAPP, effects further exacerbated by human proIAPP(KHK) overexpression. There were no observable trends with respect to ER stress.

In grafts, there was statistically significant downregulation of gene transcripts involved in ER stress and processing (and in the beta-cell markers such as Pdx1 and Ins2), likely induced by beta cell dysfunction during graft failure. Interestingly, and in agreement with these results, there were trends toward upregulation of pro-inflammatory gene transcripts.

**Summary & Future Directions:** These findings suggest that the mechanism by which proIAPP precursors mediate graft failure involves both ER stress and inflammatory pathways, but we have yet to examine relative protein levels in these pathways. This work implicates IAPP precursors as contributors to beta-cell failure during islet transplantation.

**Ellia Zhong**, Undergraduate Student  
Supervisor(s): Kirk Schultz & Amina Kariminia

Title: CD56bright NKreg cells' role in preventing relapse and GVHD

Authors: Ellia Zhong, Amina Kariminia, Avani Varshney, Kirk Schultz

### Abstract

Chronic graft-versus-host-disease (cGVHD) occurs in 50% of patients following blood and bone marrow transplant. Chronic GVHD occurs 3 months after transplant and can cause disease in any organ of the body with the most common being the skin, hair, tendons, mouth, eyes, vagina, and lungs. Even with current standards of treatment using steroids and B cell depletion drugs, patients with cGVHD, have a high mortality as well as a very high life long morbidity including cardiovascular disease, infections, mobility issues, and diabetes mellitus. Identifying biomarkers that can predict the development of cGVHD are critical as preemptive therapies to prevent cGVHD are available. Our lab has previously found that donors that have high numbers of CD56bright NKreg cells have a much lower rate of cGVHD. The phenotypic characteristic of CD56bright was found to be CD335hiCD62hi and lo in granzyme/perforin. In the present study, we hypothesize that expansion of CD56bright at 3 months after BMT would associate with less cGVHD. To have a better characterization of NK56bright cells we made a panel of different markers we used in our previous study in addition to markers recently showing importance in regards to GVHD including CXCR3. By using a 9-colour flow cytometry panel (CD62L, CXCR3, CD335, perforin, granzymeB, CD25, CD56, CD3, CD8) to study the 3 month peripheral blood samples of 62 adult BMT patients I evaluated whether CD56bright NKreg cells were associated with no GVHD. I also evaluated whether any specific sub-population of NKreg cells was important in predicting development of cGVHD. I also evaluated the impact of previous acute GVHD on the prognostic value of CD56bright NKreg cells. Our results, statistically analyzed using t-test and ANOVA at  $p < 0.05$  and  $\alpha = 0.05$ , showed significant difference of CXCR3 expression in CD56bright NKreg cells and CD56dim cells between patients who developed cGVHD and those who didn't. This biomarker likely plays a role either in the mechanism of GVHD or are activated due to processes occurring in the development of GVHD. Thus, CD56bright NKreg cells that express CXCR3 appear to be immunosuppressive and higher numbers are prognostic for the absence of future cGVHD development.

# POSTER SESSION THREE

## BASIC SCIENCE



**MODERATOR:** Michal Aharoni-Simon

**PARTICIPANTS:** Nolan Chem  
Jasmine Dhillon  
Jessica Jun  
Anna Branch  
Cody Lo  
Charles Nieh  
James Shih  
Michael Xu  
Anthony Yeung



**Nolan Chem**, Undergraduate Student  
Supervisor(s): Angela Devlin

**Title:** The role of insulin-like growth factor-1 in programming of offspring adiposity by maternal folate/vitamin B12 imbalance

**Authors:** Nolan Chem, Amanda Henderson, Angela Devlin

### Abstract

Introduction: Canada mandated fortification of folic acid of grain products to reduce the incidence of neural tube defects in 1998. Folate, an important methyl nutrient, is closely linked to the activity of vitamin B12 (B12). In Canada, folate deficiency is rare, however, approximately 1 in 20 Canadians are deficient in B12. Population studies report mothers with adequate folate/ low B12 status during pregnancy have children with greater insulin resistance and adiposity. The mechanisms underlying the relationship between maternal imbalance of folate/ B12 status and offspring adiposity and insulin resistance is not understood.

Rationale: The Devlin Lab developed a mouse model of maternal folate/B12 imbalance and reported sex-specific programming of adiposity and glucose homeostasis in adult offspring. A study recently reported that maternal B12 deficiency during pregnancy disrupts offspring growth hormone (GH)/ insulin-like growth factor-1 (IGF-1) axis, resulting in growth retardation and bone malformation. Given that GH/IGF-1 has a known role in adipose tissue metabolism, programming of offspring adiposity by maternal folate/B12 imbalance may involve disturbances in the GH/IGF-1 axis

Methods: Tissue from male and female offspring mice from dams fed a control, high folic acid with adequate B12 (HFA+B12), or high folic acid without B12 (HFA-B12) diet. Offspring were weaned onto the control diet or a western diet. Commercial ELISAs were used to quantify serum IGF-1 concentrations. Real-time PCR was used to quantify hepatic Igf1 mRNA..

Results: Female HFA-B12 offspring fed the postweaning control diet had lower serum IGF-1 concentrations than control offspring ( $p=0.002$ ) and HFA+B12 offspring ( $p=0.01$ ). Female HFA-B12 offspring fed the postweaning western diet had lower ( $p=0.08$ ) IGF-1 concentrations than HFA+B12 offspring. No effect of maternal diet on serum IGF-1 concentrations was observed in male offspring. HFA+B12 female offspring fed the postweaning western diet had higher ( $p=0.008$ ) hepatic Igf1 mRNA than control offspring.

Significance: These findings suggest a role for Igf1 in programming of offspring adiposity by maternal folate/B12 imbalance.

**Jasmine Dhillon**, Undergraduate Student  
Supervisor(s): Brad Hoffman

**Title:** Effects of Myt3 suppression in syngeneic islet transplants

**Authors:** Jasmine Dhillon, Bryan Tennant, Cheryl Whiting, Brad Hoffman

### Abstract

Introduction: Diabetes is a chronic metabolic disorder, in which pancreatic  $\beta$ -cells do not secrete sufficient insulin to maintain glucose homeostasis, which in Type 1 Diabetes (T1D) is the result of autoimmune-induced  $\beta$ -cell death. We previously identified the zinc-finger transcription factor Myt3 as being expressed in pancreatic islets and demonstrated that its suppression results in increased  $\beta$ -cell death. Although the importance of Myt3 has been established in vitro as a pro-survival factor, the long-term consequences of Myt3 suppression in vivo have not been evaluated. This study aims to examine the role of Myt3 in islet graft function and survival in a syngeneic transplant model in mice.

Methods: Control- and Myt3-transduced islets were transplanted into mice rendered diabetic by streptozotocin treatment and were monitored for body weight and blood glucose fluctuations over a 5-week period. An intraperitoneal glucose tolerance test (IPGTT) was performed prior to collecting the transplanted grafts for immunohistochemistry (IHC).

Results: Measurement of blood glucose and body weight shows that there is no physiological difference between mice receiving control- and shMyt3-transduced islets. This result is as expected for a syngeneic transplant model, and is corroborated by IPGTT, which shows that both control- and shMyt3-transduced islets are able to respond to a glucose load and establish normoglycemia within 2 hours. IHC analysis comparing the number of insulin-positive ( $\beta$ -cells) and GFP-positive (transduced cells) cells in control- and shMyt3-transduced grafts shows that there is a significantly reduced number of GFP-positive cells in the shMyt3 graft. In addition, the overall architecture of the control and shMyt3-transduced grafts, analyzed by staining for insulin-positive and glucagon-positive ( $\alpha$ -cells) cells, is unaffected by either treatment. Taken together, these data suggest that there is increased cell death in shMyt3-transduced islet grafts.

Conclusions: Physiological findings suggest that although Myt3 is required for islet cell survival, suppression of Myt3 in syngeneic islet transplants does not have an effect on the establishment of normoglycemia compared to the control. IHC results indicate that suppression of Myt3 leads to transduced-cell death, as was seen in previous in vitro experiments. These results implicate Myt3 as a potential therapeutic target for the treatment of T1D.

**Jessica Jun**, Undergraduate Student  
Supervisor(s): Todd Woodward

**Title:** The functional connectome: Analysis of network activation in psychosis patients across speech-related tasks

**Authors:** Jessica Jun, Nicole Sanford, Paul Metzack, Katie Lavigne, Paul Allen, Mathilde Antoniades, Todd Woodward

### Abstract

**Background:** The Functional Connectome project aims to compile and analyze shared neuroimaging data in order to define the functional networks underlying hallucinations and provide insights into the biological underpinnings of schizophrenia and its positive symptoms. In previous analyses, hyperactivity in a language-based network and hypoactivity in the default-mode network have been observed in hallucinating patients during passive perception of language-based stimuli, but not during active manipulation of verbal material or non-linguistic language perception of language-based stimuli.

**Hypotheses:** In the current study, we are using source monitoring and verbal fluency tasks as examples of controlled speech. We expect to find spatial replication and temporal non-replication of the previously-observed pattern of network activation across tasks, with no differences between hallucinating and non-hallucinating groups. When these datasets are merged with data from a previous task involving uncontrolled speech, however, we expect to find hyperintensity in the hallucinating group.

**Methods:** The source monitoring dataset involves 63 subjects (25 patients, 38 controls) who, after participating in two task conditions (a reality monitoring task and a source monitoring control task), completed recall testing in the fMRI scanner. The verbal fluency analysis dataset involves 68 subjects in 3 groups: UHR (ultra high risk for psychosis), FEP (first-episode psychosis), and control; and 2 task conditions involving generation of verbal material in response to language-based stimuli (easy and hard), which were completed in the fMRI scanner. Brain activity measured in both tasks represent network activation in response to active manipulation of verbal material. The datasets are being analyzed both separately and as merged data using CPCA (Constrained Principal Component Analysis).

**Preliminary Outcomes:** Two networks were identified from the source monitoring analysis, corresponding to a task-positive network and the default-mode network, and no significant differences in network activity were found between groups. Three components have been extracted from the verbal fluency analysis. Merged analyses of the datasets are ongoing.

**Significance:** Imaging task-based networks across tasks involving both controlled and uncontrolled speech will improve our understanding of schizophrenia and help identify biological and cognitive phenotypes. From a methodological perspective, we can perform more powerful analyses by merging multiple datasets.

**Anna Branch**, Undergraduate Student  
Supervisor(s): Francis Lynn & Nicole Krentz

**Title:** Overexpression of the cell cycle inhibitor p27 drives differentiation of pancreatic endocrine cells

**Authors:** Anna Branch, Nicole Krentz, Francis Lynn

### Abstract

Diabetes mellitus, which affects 387 million people worldwide, involves the lack or dysfunction of endocrine beta cells in the pancreas. Treatment has been proposed to replace these cells with beta cells generated through directed differentiation of human embryonic stem cells. However, not enough is known about the process by which endocrine cells differentiate naturally to put this into effect. It is known that a subset of pancreatic progenitor cells give rise to Ngn3+ endocrine progenitor cells, which differentiate into the hormone producing alpha, beta, delta, PP, or epsilon endocrine cells. Previously in our lab, we demonstrated that there is a correlation between lengthening of the cell cycle and differentiation of endocrine cells during mouse pancreas development. Thus, we hypothesized that overexpressing p27, a cyclin-dependent kinase inhibitor that lengthens the cell cycle, would drive differentiation of pancreatic progenitor cells into mature endocrine cells. Using a transgenic mouse model to specifically overexpress p27 in the developing pancreas from embryonic day (E)10.5-E12.5, we injected pregnant mice with EdU, a nucleotide analog that labels cycling cells, and quantified the number of EdU+ cells. In control embryos at E12.5, the proportion of EdU+ cells after 3.5 hours of labeling was  $0.38 \pm 0.03$  and was significantly reduced to  $0.29 \pm 0.02$  in transgenic embryos, suggesting that p27 overexpression lengthens the cell cycle in pancreatic progenitors. To understand the consequences of p27 overexpression, the number of cells immunopositive for markers of differentiated cells was quantified. Shortly after p27 overexpression, the number of cells expressing Ngn3, a pro-endocrine factor that is required for differentiation, increased 2.7-fold. In addition, the proportion of glucagon-expressing alpha endocrine cells increased 2.5-fold. These results demonstrate that overexpression of p27 drives differentiation of pancreatic cells by lengthening the cell cycle and that cell cycle lengthening is not only correlated with differentiation, but also causative. Understanding the methods by which mature endocrine cells develop naturally in vivo and discovering a method to drive differentiation could be very useful in directing the differentiation of stem cells into mature beta cells used to treat diabetes.

**Cody Lo**, Undergraduate Student  
Supervisor(s): Daniel Goldowitz

**Title:** Application of the FANTOM5 time-course CAGE data to determine key regulators for cerebellar development

**Authors:** Cody Lo, Thomas Ha, Peter Zhang, Abhishek Mishra, FANTOM5 Consortium, Daniel Goldowitz

### Abstract

Introduction: Neural development depends on the differential expression of various genes over time. Given recent advancements in genomics, large-scale transcriptome analyses can evaluate differential expression of many genes temporally. In particular, the FANTOM5 (Functional Annotation of the Mammalian Genome) project has analyzed gene expression in 19 human and 14 mouse time-courses across multiple cell types, thus offering one of the most robust data sets available to date.

Objectives: Using the FANTOM5 time-course data, we aim to identify key regulators in cerebellar development and experimentally validate our results to confirm the reliability of such large-scale transcriptome analyses.

Methods: The first step in determining candidate genes included finding differentially expressed transcription factors in the FANTOM5 time course data. These genes were then sorted by maximum expression and were eliminated if they had a known knockout phenotype in the cerebellum. The expression profiles of the remaining candidate genes were determined using qRT-PCR and compared to profiles predicted by the FANTOM5 database. Using in utero shRNA transfection, all candidate genes were knocked down at E12 (embryonic day 12) and phenotype observed at E15 and E18.

Results: Analysis of the FANTOM5 cerebellar time course data produced 1218 differentially expressed transcription factors. The candidate selection process produced 10 possible genes for further analysis. Expression profiles for the candidate genes produced by qRT-PCR were similar to those predicted with the FANTOM5 data set. The in utero shRNA transfection at E12 showed all gene knockdowns to display normal development at E15. Interestingly, when visualized at E18 the ATF4, SCRT2 and RFX3 knockdowns all displayed a developmental phenotype. The phenotype for all three genes included a reduction of tissue size and delay in overall development.

Conclusions: The developmental phenotype produced by ATF4, SCRT2 and RFX3 suggest they are key regulators in cerebellar development. The similar phenotype amongst the genes suggests they share a similar mechanistic pathway. Preservation of normal development at E15 suggests the regulatory role of these genes does not become prominent until E16 or E17. Further experiments will be conducted at these time points to further elucidate their role in development.

**Charles Nieh**, Undergraduate Student  
Supervisor(s): Bruce Verchere

**Title:** Measurement of islet amyloid polypeptide (IAPP) precursors as a biomarker for early diabetes development

**Authors:** Charles Nieh, Jaques Courtade, Paul Yen, Bruce Verchere

### Abstract

Type 2 diabetes (T2D) is characterized by insufficient pancreatic beta cell mass and hyperglycemia, and it is highly prevalent in populations throughout the world. In healthy, functional, beta cells, proinsulin is synthesized and cleaved by the enzymes prohormone convertase (PC)1/3 and PC2 to generate insulin. During T2D progression, patients accumulate higher levels of proinsulin relative to insulin, suggesting a potential defect in prohormone processing in the beta cells. Beta cells also secrete islet amyloid polypeptide (IAPP), which is derived from proIAPP and also cleaved by PC1/3 and PC2. Given the impaired proinsulin processing in T2D, we predict that there is likely an impairment in proIAPP processing in these patients as well, which may be measured by the ratio of proIAPP to mature IAPP. To demonstrate our hypothesis, we are developing an ELISA to detect IAPP precursors in circulation and utilizing this assay in T2D patients.

Using antibodies raised against human proIAPP fragments, we developed a sandwich immunoassay to specifically detect the IAPP precursors proIAPP(1-67) and proIAPP(1-48). At the same time, we utilized synthetic forms of these peptides to determine if our antibodies are capable of detecting the precursor forms. Lastly, we spiked known concentrations of our synthetic peptides into a plasma matrix and performed a spike and recovery analysis to validate our platform.

Preliminary data reveals that using synthetic proIAPP(1-67) and proIAPP(1-48), we can generate a standard curve and we were able to optimize the concentration of capture and detection antibodies. Using fetal bovine serum to mimic the human plasma matrix, we obtained spike recovery values nearing 100%, suggesting that we may be able to accurately measure the concentration of these peptides in human plasma. We determined respective cross-reactivity values for proIAPP(1-67), proIAPP(1-48) and mature IAPP to be 60%, 100% and 0%, demonstrating our ability to specifically measure IAPP precursors only. Once validated, we will use the ELISA to measure concentrations of IAPP precursors in T2D individuals versus healthy controls.

This work may implicate IAPP precursors as novel biomarkers of T2D development and may also have applications in the context of T1D and for measuring the effectiveness of islet transplantation.



**James Shih**, Undergraduate Student  
Supervisor(s): Stefan Taubert

**Title:** Characterising transcription factor partners of the Mediator subunit CDK-8 in the developmental and physiological responses of *C. elegans*

**Authors:** James Shih, Jennifer Grants, Anik Muhuri, Stefan Taubert

### Abstract

The regulation of eukaryotic transcription is a finely tuned process that involves a complex interplay between Transcription Factors (TFs) and RNA Polymerase (RNAP), which are brought together physically by transcriptional coregulators to initiate transcription. The Mediator complex is a well-characterised coregulator, its activity being globally required for transcription of all genes. However, certain subunits of Mediator have also been shown to activate or repress genes involved in specific physiological pathways. These responses are mediated by binding of a specific TF to a Mediator subunit, but in many cases the Mediator-TF interactions underlying such responses remain to be identified. One gene program-specific Mediator subunit is CDK-8 (Cyclin Dependent Kinase 8). Microarray analysis of *cdk-8* null mutants in the nematode *Caenorhabditis elegans* revealed differential expression of two subsets of genes: genes involved in the Epidermal Growth Factor Receptor (EGFR) signalling pathway, which plays critical roles in development and tumorigenesis; and detoxification genes involved in the physiological response to the toxic heavy metal cadmium. Our goal has been to characterise the molecular mechanisms of CDK-8 regulation in both the EGFR and the cadmium response pathways: to this end, we investigated which TFs interact with CDK-8, and at which specific regulatory sequences. Previous genetic epistasis analyses established two such TFs: in the EGFR pathway, the TF *lin-1* required CDK-8 for transcriptional repression; meanwhile, in the Cadmium Response pathway, the GATA-type TF *elt-2* required CDK-8 to induce transcription of *cdr-1*, a cadmium detoxification gene. To further characterise the interactions between these TFs and CDK-8, we aim to study protein-protein interactions between CDK-8 and the two candidate TFs, LIN-1 and ELT-2, using Yeast-Two Hybrid Assays. Meanwhile, to further characterise the biological significance of ELT-2 activity in the Cadmium response, we are performing Site-directed Mutagenesis on the GATA elements of the *cdr-1* promoter to examine whether loss of ELT-2 binding on the *cdr-1* promoter will result in decreased resistance to Cadmium. Taken together, our current data suggests that the Mediator subunit CDK-8 plays essential roles in regulating specific physiological and developmental programs.

**Michael Xu**, Undergraduate Student  
Supervisor(s): Glen Tibbits

**Title:** Molecular mechanisms of electrogenesis in the neonate heart: Etiology of junctional ectopic tachycardia

**Authors:** Michael Haoying Xu, Cici Chenliu, Helen Sheng, Chi Hung Chen, Glen Tibbits

### Abstract

Junctional Ectopic Tachycardia (JET) is a supraventricular arrhythmia that develops in neonates following open heart surgery. Patients with JET exhibit atrioventricular dissociation, a narrow QRS complex, and an accelerated ventricular rhythm above 160 bpm. Various factors may contribute to the onset of JET, such as duration of cross clamp time, a young age, and mechanical damage to the AV region but the etiology of JET is still unknown. We previously demonstrated that younger, 10 day old rabbit Atrioventricular Nodal (AVN) cells were more susceptible to ischemic reperfusion (I/R) injury than older, 56 day old rabbit cells, while both 10 day and 56 day old Sinoatrial Nodal cells were unaffected by I/R. Clinical data also suggested a correlation between prolonged ischemia duration and development of JET, thus we hypothesized that I/R injury to the AV region in particular is the principle mechanism in the etiology of JET. The goal of this project then, is to study the effect of I/R on AVN function in an intact heart.

To study the effects of I/R on an intact rabbit heart, we used optical mapping techniques on Langendorff perfused 10-day and 56-day old rabbit hearts. We isolated the heart from the rabbit and performed retrograde perfusion using Krebs–Henseleit Buffer until the blood cleared out. The heart was then loaded with a potentiometric dye and a Ca<sup>2+</sup> sensitive dye, followed by perfusion with a hypercalcemic, acidotic solution. This was then followed by 30 minutes of global ischemia, then reperfused with the aforementioned Krebs-Henseleit Buffer. Data was analyzed using a program written in the Interactive Data Language environment, focusing primarily on the cardiac rhythm following global ischemia.

Our preliminary results from the optical mapping show that out of 20 10-day hearts, 5 developed JET-like arrhythmia while 12 developed AV block. In contrast, all of the 56 day old hearts remained in sinus rhythm following I/R injury. These results thus far support our hypothesis.

Future directions will involve a similar protocol with optical mapping focusing primarily on the AVN region following ischemic reperfusion.

**Anthony Yeung**, Undergraduate Student  
Supervisor(s): Catherine Pallen

**Title:** The role of PTP $\alpha$ -dependent Akt signalling in oligodendrocyte differentiation

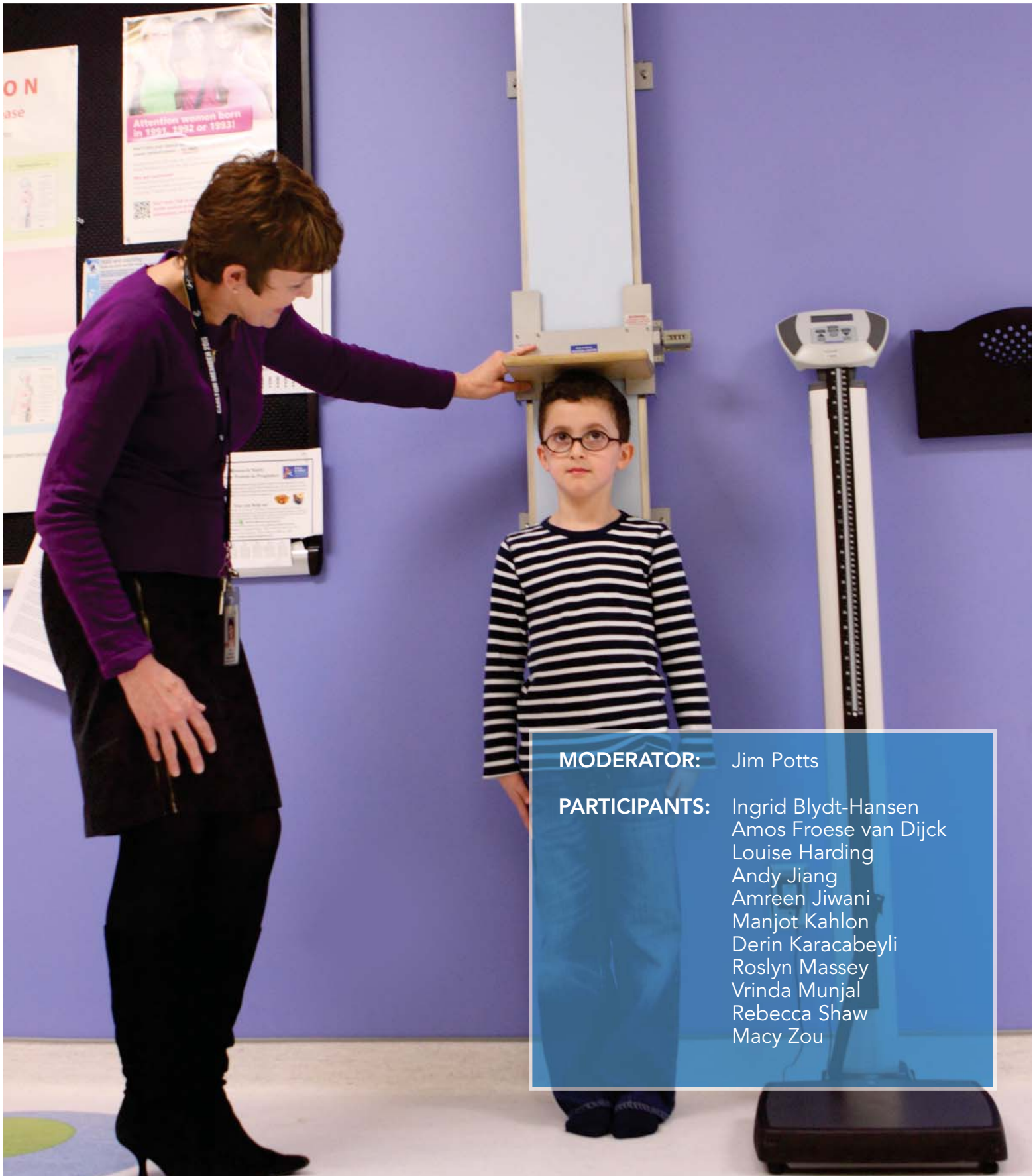
**Authors:** Anthony Yeung, Philip T Ly, Arshdeep Marwaha, Catherine J Pallen

### Abstract

Receptor-like protein tyrosine phosphatase PTP $\alpha$  is an important regulator of many cellular processes, including differentiation of oligodendrocyte progenitor cells (OPCs) into mature oligodendrocytes (OLs), which mediate myelination in the central nervous system. Previously, our lab demonstrated that OPCs lacking PTP $\alpha$  expression (PTP $\alpha$  knockout, KO) have defective differentiation as, compared to WT OPCs, fewer KO OPCs progress to express the mature OL marker myelin basic protein (MBP) and acquire the complex cell morphology typical of mature OLs. Furthermore, activation of the serine/threonine kinase Akt is also reduced in differentiating KO OPCs, indicating that PTP $\alpha$ -dependent Akt signalling may be important for OL development and myelination. Our current studies aim to remediate differentiation defects in KO OPCs by applying pharmacological reagents that can enhance Akt activation. We are currently testing the growth factor neuregulin 1 (NRG1) and the PTEN inhibitor VO-OHpic (VO), both potent activators of Akt signalling. First, we validated the ability of these compounds to promote Akt activation in a mouse OPC cell line (Oli-neu cells). We showed that in differentiating Oli-neu cultures, NRG1 but not VO increased Akt activity as measured by the extent of Akt phosphorylation on Ser473. We also examined whether NRG1 and VO can remediate PTP $\alpha$ -dependent OPC differentiation. Primary OPC cultures derived from WT and KO mouse embryonic neural stem/progenitor cells were treated with NRG1 and VO for 5 days under differentiation conditions. The extent of OPC differentiation was determined by quantifying the population of OL lineage cells (Sox10) that formed mature OLs (MBP+). Our preliminary findings indicate that VO treatment has no effect on Akt activation in differentiating WT and KO OPC cultures and no significant effect on OPC differentiation. On the other hand, NRG1 treatment for 5 days stimulates Akt activation and differentiation in WT OPCs, but not in KO OPCs. This indicates that NRG1 promotes OPC differentiation by a PTP $\alpha$ -dependent mechanism. These findings will enhance our understanding of the signalling pathways that orchestrate OPC differentiation, which is necessary for the development of novel molecular targeted therapies to treat demyelinating diseases and various pediatric leukodystrophies.

# POSTER SESSION FOUR

## CLINICAL



**MODERATOR:** Jim Potts

**PARTICIPANTS:** Ingrid Blydt-Hansen  
Amos Froese van Dijck  
Louise Harding  
Andy Jiang  
Amreen Jiwani  
Manjot Kahlon  
Derin Karacabeyli  
Roslyn Massey  
Vrinda Munjal  
Rebecca Shaw  
Macy Zou

**Ingrid Blydt-Hansen**, Undergraduate Student  
Supervisor(s): Clara van Karnebeek & Gabriella Horvath

**Title:** Genomic analysis for revealing the underlying molecular defect in treatment-responsive neuropsychiatric patients with abnormal CSF neurotransmitter profiles

**Authors:** Ingrid Blydt-Hansen, Maja Tarailo-Graovac, Casper Shyr, Linhua Zhang, Graham Sinclair, Hilary Vallance, Colin J Ross, Wyeth Wasserman, Gabriella Horvath, Clara D M van Karnebeek

### Abstract

Overview: Patients with primary neurotransmitter abnormalities may present with movement disorders, psychiatric/behavioral disturbances, autonomic symptoms, axial hypotonia and developmental delay. In 15 patients with abnormal levels of CSF dopamine and serotonin metabolites (HVA and 5-HIAA), known congenital neurotransmitter deficiencies have been eliminated through further biochemical testing, proposing the neurotransmitter abnormality is secondary to another underlying unknown cause. Most patients had a trial of neurotransmitter replacement therapy. Identifying the underlying gene defect could help to better understand the pathophysiology of the secondary neurotransmitter deficiencies.

Hypothesis: Whole Exome Sequencing (WES) may identify a genetic defect in treatment-responsive patients with neuropsychiatric phenotypes and abnormal neurotransmitter profiles in whom known congenital neurotransmitter deficiencies have been ruled out.

Methods/Results: This study was approved by the University of British Columbia and Children & Women's Ethics Board (CW12-0019/H12-00067). Chart reviews were performed to collect information on medical history, physical exam, investigations, response to treatment and molecular defects of 15 patients (male and female, ages 2.5 to 50 years) with secondary neurotransmitter abnormalities. Thorough review of patient's clinical pictures provided information on treatment response to L-dopa/carbidopa and 5-hydroxytryptophan treatments. Many patients showed a favourable response to neurotransmitter replacement therapy, with one patient's movement disorder exacerbated by treatment. Certain patients had gene defects not previously reported to be associated with abnormal CSF neurotransmitter levels (BRAF, SCN2A, CSTB). Further investigation into these genes' function helped in formulating a hypothesis on how these defects may contribute to secondary neurotransmitter abnormalities.

Conclusions: Largely favourable response to neurotransmitter replacement therapy (dopamine and serotonin supplementation) demonstrates that regardless of the underlying gene defect, patients should get a trial of therapy. WES results helped to identify the gene defects in most of these patients, in addition to formulating a hypothesis and investigations in the gene's involvement in the biogenic amine metabolic pathways.

Significance: By investigating the genetic basis and pathophysiology of the secondary neurotransmitter deficiencies, we understand a single patient's condition, but this knowledge can be applied to other patients to improve their outcomes through better treatment. This study is also broadening the existing phenotypic spectrum for existing genetic conditions.

**Amos Froese van Dijck**, Undergraduate Student  
Supervisor(s): Zoe Brown

**Title:** A randomized controlled pilot study to examine the effects of goal-directed fluid therapy on post-operative outcomes in children undergoing scoliosis repair

**Authors:** Amos Froese van Dijck, Zoe Brown, Matthias Gorges

### Abstract

**Background:** Scoliosis correction surgery is a major procedure performed in adolescents. It can be associated with severe blood loss and hypotension, which can be difficult to manage; anesthesiologists use fluids and vasopressors to optimize blood pressure and organ perfusion during surgery. In adults, intraoperative fluid management has been shown to effect postoperative outcomes, such as LOS and SSIs. Goal Directed Therapy (GDT) is a method whereby administration of fluid is patient specific, using a measure of cardiac output (CO), e.g. via transesophageal Doppler. Currently the timing and amount of fluid given in scoliosis surgery is guided by clinical experience, CO measurements and changes in spinal cord monitoring due to surgeons request. Interestingly fluid management seems to differ between anesthesiologists and patients, which could correlate with incidence of post-operative complications (such as acute kidney injury (AKI)), potentially preventable through GDT.

**Objective:** The aim of this study is to compare the effectiveness of GDT to standard anesthetic fluid management in a randomized controlled pilot trial. Main outcomes of interest are postsurgical kidney dysfunction, prevalence of intra-operative hypotension, volumes of administered fluids, and length of hospitalization. We hypothesize that GDT decreases the incidence of intra-operative hypotension and spinal cord monitoring changes by 10-20%, AKI by 25%, and length of hospitalization by 24hrs.

**Methods:** With parental consent and patient assent 40 patients with idiopathic scoliosis will be recruited and randomized to GDT or standard of care. In the intervention group, fluid boluses will be given when either mean arterial pressure or stroke volume drops below 15% from baseline. In the control group, fluid boluses will be given at the anesthesiologist's discretion. Amount and type of fluids and drugs given intraoperatively, urine output, and vital signs during the procedure and for the first 48 hours post-operatively will be recorded. Data will be analyzed using R.

**Results:** Preliminary data from 4 patients (median age 16.75, 3 female) is available. Fluid amounts were 2800ml and 2918ml during GDT, and 3400ml and 2150ml in standard of care. Creatinine changes were 3.6% and 15.6% in GDT and 11.1% and 5.9% in standard of care. Biomarker results of AKI are pending.



**Louise Harding**, Undergraduate Student  
Supervisor(s): Anton Miller

**Title:** Behaviour concerns in children with neurodevelopmental disorders and disabilities

**Authors:** Louise Harding, Anton Miller, Emily Gardiner

### Abstract

Background: Neurodevelopmental disorders and Disabilities (NDD/D) are a heterogeneous group of brain-based conditions (such as autism, cerebral palsy and intellectual disability), which compromise children's ability to acquire needed skills in developmental domains such as speech-language, motor, cognitive and adaptive. Behaviour problems occur more frequently in children with diagnosed NDD/D than among typically developing children, and can significantly impact the quality of life of caregivers and families.

Aims: 1) To document the frequency and types of behaviour concerns that parents discuss with subspecialist pediatricians in the course of developmental consultations at a regional and provincial assessment centre, Sunny Hill Health Centre for Children (SHHCC);

2) To examine how different kinds of behavioural concerns are distributed across a range of specialized clinics serving ostensibly distinct populations within SHHCC.

Setting & Data Source: Information on behavioural concerns was obtained through retrospective review of reports prepared by SHHCC developmental pediatricians (n = 12) and pediatric physiatrists (n=1) following assessment in each of the following clinics: Hearing Loss (children with permanent hearing loss suspected of having additional developmental concerns); Autism (diagnostic assessments for autism spectrum disorder); Brain Injury (follow-up of acquired brain injury); and Complex Developmental-Behavioural Conditions Clinic (complex presentations). Eligible subjects were those between 3 and 8 years of age, seen between May 1, 2012 and April 30, 2014.

Data Management and Analysis: Parent concerns were extracted verbatim from 198 reports. After a team-based data cleaning session, a concept sorting method with no a priori planning was used to organize the extracted concerns into thematic categories as agreed by the 3 research team members, followed by labeling of the groupings that emerged. Preliminary results will be presented. Quantitative analysis techniques will analyze trends in the distribution of these behavioural categories across clinics.

Expected Outputs and Significance: It is expected that there will be consistencies in the concerns reported across the diverse clinics, indicating that there may be behaviours which are characteristic of NDD/D as a group. This exploration is intended to contribute to a departure from the "diagnose-and-treat" model of NDD/D.



**Andy Jiang**, Undergraduate Student  
Supervisor(s): Ian Pike

**Title:** The social and economic burden of poisonings in British Columbia

**Authors:** Andy Jiang, Fahra Rajabali, Roy Purssell, Ian Pike

### Abstract

Background: Injuries are the leading cause of death for Canadians aged 1 – 44, placing a tremendous burden on the healthcare system and society. Each day, an average of 10,000 people require medical attention due to preventable injuries. In particular, injuries due to drug poisoning surpass motor vehicle collisions in the US as the leading cause of injury death. Previous studies have primarily focused on understanding the magnitude of the problem, but few have analyzed the wider social and economic effects of poisonings.

Aims: (1) To identify poisoning mortality and morbidity trends in BC for the period 2007 to 2013 by age, sex, substance, intent, and geography, (2) To identify possible correlations between medication prescriptions and poisoning trends in BC, and (3) To determine the annual economic cost of poisonings in BC for the year 2013.

Data Sources: Poisoning mortality and morbidity data for the period 2007 to 2013 was obtained from: (1) BC Vital Statistics, (2) BC Discharge Abstracts Database, (3) BC Drug and Poison Information Centre Database, (4) BC Ambulance Services, (5) National Ambulatory Care Reporting System, (6) Vancouver Coastal Health Emergency Department Database, and (7) BC PharmaNet.

Methods: Data will be analyzed to identify poisoning mortality and morbidity trends (hospitalizations, emergency department visits, ambulance transfers, calls to the drug and poison information centre) by age, sex, intent, location, and substance type. BC PharmaNet data will be analyzed for the significance of any correlations between drug prescription and poisoning trends in BC. The economic burden in 2013 will be estimated by considering both direct costs (e.g. hospital costs) and indirect costs (e.g. lost productivity) to society.

Outcomes & Relevance: Findings from this study will identify populations at elevated risk for poisoning in BC, in order that targeted prevention efforts can be developed and implemented to reduce the burden of poisoning on society. Broader outcomes include determining the requirements for a BC poisoning surveillance system, and informing the development of poison control policies and interventions.

**Amreen Jiwani**, Undergraduate Student  
Supervisor(s): Rajavel Elango

**Title:** Validation of the 13C- Phenylalanine breath test in children with Phenylketonuria (PKU)

**Authors:** Amreen Jiwani, Gayathri Murthi, Abrar Turki, Rajavel Elango

### Abstract

Phenylketonuria (PKU) is an autosomal recessive genetic disorder that results in the build up of the amino acid phenylalanine (Phe) in the blood (Williams et al., 2008). Elevated levels of phenylalanine have caused growth impairments and cognitive developmental delays. Recently, a labeled breath test, using 1-13C- Phenylalanine (1-13C-Phenylalanine Breath Test, 13C-PBT) has been developed to measure Phenylalanine metabolism in patients with PKU (Turki et al., 2015). This test, exploits the hepatic enzyme, phenylalanine hydroxylase (PAH) and its ability or inability to convert phenylalanine into tyrosine, in order to obtain whole body phenylalanine oxidative capacity, as an in vivo indicator of PAH activity (Okano et al., 2004). The previous study conducted on PKU patients, measured rates of Phe oxidation, via labeled breath tests, prior to and post intervention with Kuvan<sup>®</sup>, [which serves as ] a cofactor [for] PAH. The results found that Phe oxidation rates after intervention increased in 6 of the 9 children who responded to Kuvan<sup>®</sup> treatment (Turki et al., 2015). Currently, the primary objective of this study is to re-examine phenylalanine metabolism in four previously studied children aged 11, 17, 17 and 19 years of age with PKU using 13C -PBT, in order to determine the repeatability and reproducibility of the test (as a % of dose). This repeated measures test will take into account growth and development of the child, and indicate if this affected 13C-PBT values. It is hypothesized that the 13C-PBT will have good reproducibility (between 5-10 % from a clinical significance point of view). Currently data collection and analysis is on going. We hope that the phenylalanine breath test will be a clinically useful tool for routine monitoring and management of children with PKU.

**Manjot Kahlon**, Undergraduate Student  
Supervisor(s): Kelly Brown

**Title:** Measuring immune activation in tears to improve monitoring and outcomes for childhood uveitis

**Authors:** M Kahlon, K Morishita, K L Brown

### Abstract

Each year, about 40 to 50 children in BC will develop uveitis, a condition characterized by inflammation in the uvea of the eye. The exact cause of uveitis is unknown, but it is non-infectious and appears to be autoimmune or autoinflammatory in nature because it is most common in children with the autoimmune condition, juvenile idiopathic arthritis (JIA). For children at high risk of developing uveitis, standard JIA care guidelines were altered in 1993 to include periodic slit-lamp examinations by an ophthalmologist in order to detect and monitor uveitis. While this method can indicate if the disease is present or absent, it is unable to predict the onset, course or severity of uveitis. Therefore, the purpose of this study is to generate preliminary data that might support a new, non-invasive method to obtain and analyze eye tears for putative biomarkers of uveitis.

Tears will be collected from healthy individuals and children with active uveitis and/or JIA to be comparatively analyzed for inflammatory markers by multiplex and standard ELISA. Standard inflammatory cytokines associated with ocular disease will be investigated and particular attention will be paid to two novel inflammatory agents: S100A12 and hyaluronan (HA), that are present in tears and elevated with ocular and autoimmune inflammation. S100 proteins have been shown to track with disease activity and improve outcomes in childhood inflammatory conditions. HA in its native high molecular weight form is a lubricant and major constituent of the eye, however, coincident with inflammation, HA is fragmented into low molecular weight forms that promote inflammation.

Our working hypotheses are that inflammation is best monitored at the source (ie, in the eye) and tears obtained from patients with active uveitis will contain a defining pattern of inflammatory markers. Identification of a panel of potential biomarkers of uveitis may improve screening and management of uveitis not just at BCCH but in all service centres in BC, even in remote areas that are not serviced by a pediatric ophthalmologist.

**Derin Karacabeyli**, Undergraduate Student  
Supervisor(s): Shazhan Amed

**Title:** Adapting and adopting the Live 5-2-1-0 Family Physician Toolkit: A pilot study to facilitate health promotion through primary care

**Authors:** Derin Karacabeyli, Stephanie Shea, Susan Pinkney, Ilona Hale, Erna Jensen, Shazhan Amed

### Abstract

**Background:** The prevalence of childhood obesity continues to be a major public health concern. SCOPE is a childhood obesity prevention initiative that partners with communities across BC and uses the Live 5-2-1-0 message (5+ vegetables and fruits/day; <2 hours of screen time/day; 1+ hour(s) of active play/day; 0 sugar-sweetened drinks) across multiple sectors to help make healthy choices easier for children. To enhance health promotion through the primary care setting, SCOPE created and piloted the Live 5-2-1-0 Family Physician (FP) Toolkit in one of its partner communities. Based on the findings from that initial pilot study, the toolkit intervention is currently being adapted, implemented, and evaluated in a new SCOPE partner community.

**Objectives:** To adapt and pilot the Live 5-2-1-0 FP Toolkit in a new Live 5-2-1-0 community in order to:

- 1) Enhance FPs' capacity to routinely assess and manage BMI in pediatric patients by facilitating collection of BMI data through a self-care BMI station; and
- 2) To deliver health promotion messages to children/families in the primary care setting.

**Methods:** Pre-post observational study design, where data is being collected through FP surveys, family surveys, Healthy Habits Questionnaires, and FP semi-structured qualitative interviews.

**Baseline Results:** The majority of FPs (N=9) agreed that consistent BMI tracking is important; however, in practice, they were not routinely tracking BMI. A discrepancy also existed between FP beliefs and self-efficacy. While 78% of FPs agreed that motivational interviewing could be a powerful tool to help with behaviour change, only 33% felt comfortable using this technique. Among families, awareness of health promotion messages related to Live 5-2-1-0 in the clinic was low.

**Implications:** Baseline results highlight areas where the Live 5-2-1-0 FP Toolkit may benefit FPs and pediatric patients/families. The intervention has the potential to enhance physicians' capacity to routinely assess and manage BMI, sensitively discuss weight with families using motivational interviewing, and raise families' awareness of Live 5-2-1-0-related health messages in the clinic.

**Roslyn Massey**, Undergraduate Student  
Supervisor(s): Guy Dumont & Chris Petersen

Title: Developing an EEG simulator

Authors: Roslyn Massey, Chris Petersen, Matthias Gorges, Mark Ansermino

### Abstract

Depth of hypnosis (DoH) monitors display real-time readings of a patient's electroencephalogram (EEG) during surgery. DoH monitors help to mitigate inter-patient variability by allowing the anesthetist vary the drug titration based on the patient response. There are many types of these monitors commercially available, but there is no standard algorithm or running parameters. The monitors output an EEG reading on dimensionless index from 100 (awake) to zero (comatose), but do not account for different anaesthetic agents, or different measurement conditions.

This project developed a prototype EEG simulator that can be controlled from a connected smartphone or computer. This simulator will be incorporated into an app. This app will be used to test the efficacy of DoH monitors, and that can be used to perform a comparative study of three depth of hypnosis monitors the BIS (Covidien, IR), Entropy (GE HealthCare, UK) and NeuroSENSE(NeuroWave Inc, OH)

A mathematical model was used to generate the EEG like signals. This model used a seeded random number series, an amplitude scaling factor time  $t$ , and the variable parameter  $k$  to produce an eeg-like waveform. This waveform is then turned into sound using a digital to analog converter, and transmitted to the monitors via the audiojack of a smartphone. The monitors process the signal as they would EEG, and produce a reading. Varying the parameter  $K$  affects the frequency and other factors, resulting in a change in output DoH value. A  $k$  value for each DoH on each monitor was determined, creating a map relating depth of hypnosis to parameter  $k$ . The app will utilize this map by outputting the parameter  $k$  value waveform for a selected depth of hypnosis. This waveform is then transmitted to the monitor and processed, and the resulting DoH out-putted by the monitor is compared to the selected DoH value. If the monitor is effective, they will be the same. For each monitor, a sweep of parameter  $k$  from 0.4 to 6.5 was performed. This was to encompass all of the DoH values, and would also highlight the differences between the monitors.

The sweep was able to create a map for the Entropy and the Neurosense, but not for the BIS. The BIS was unable to process the simple waveform as it would real EEG. Future directions for this project would be to evaluate the differences in the monitor maps, and to determine why the BIS monitor did not process the waveform adequately.

**Vrinda Munjal**, Undergraduate Student  
Supervisor(s): Naznin Virji-Babul

**Title:** Development of an assessment tool for evaluating risk of concussion in sports organizations

**Authors:** Vrinda Munjal, Arnold Yeung, Eoin Bates, Nazlin Nathu, Naznin Virji-Babul

### Abstract

Sports related concussions can result in impairments in physical, cognitive and emotional function. The risk for repeated injury, particularly in contact sports is high and the implications of multiple concussions in children and adolescents, whose brains are still under development, may be significant. Our objective is to develop a tool that can define key risk factors and quantify the relative risk of each factor in specific sports.

We identified sport-specific risk factors by conducting a thorough literature review, and compiled a list of concussion safety policies and concussion awareness tools. Based on our exhaustive review, we developed a risk assessment algorithm based on a modified version of an engineering risk assessment tool known as the Failure Mode and Effects Analysis (FMEA). The probability and severity of concussion for each included risk factor was extracted from literature and translated as variables for the FMEA. Using assessed scores of the conditions of sports organizations, risk priority numbers (RPN) for each risk factor were proposed as a quantitative measure of the criticality of its associated risk.

The risk factors for hockey organizations and their associated variables have been calculated from statistical data obtained from concussion literature. When implemented in a hockey organization, the tool would be able to assess the organization's current risk of a concussion occurring and the severity of that concussion.

This tool can be tailored to represent an individual's risk of concussion by modifying certain risk factors. This may allow the individual to make changes to their gameplay to ensure safety. In addition, this tool can be modified and used to analyze the risk of other sports related or work related injuries.

We will validate the preliminary algorithm by using test cases from litigation court documents and field-testing in representative sports organizations so that further refinements can be made. Using these RPNs, organizations may mitigate concussion risk based on the critical risk factors identified by improving their associated scores through modifying risk factors and implementing policy changes. RPNs would then be updated to represent these modifications.

**Rebecca Shaw**, Undergraduate Student  
Supervisor(s): Anna Lehman

**Title:** Gene discovery for vocal cord paralysis

**Authors:** Rebecca Shaw, Cristina Dias, Jeffrey Ludemann, Rosemarie Rupps, Vance Tsai, Anna Lehman

### Abstract

**Background:** Familial congenital vocal cord paralysis is a very rare disorder that can cause upper airway obstruction and severe respiratory distress in infants. In many cases of familial vocal cord paralysis, the genetic origin is never identified. We present a non-consanguineous family of European descent with five members across two generations who are affected with congenital vocal cord paralysis. Two of the affected family members also have congenital bilateral clubfoot. A review of the literature revealed that the combination of congenital vocal cord paralysis and congenital bilateral clubfoot in the absence of any other abnormalities has previously been reported only once by Morelli et al. in 1982.

**Hypothesis:** Autosomal dominant familial vocal cord paralysis presenting with congenital clubfoot is caused by mutation of a gene involved in neuromuscular development.

**Methods:** Whole exome sequencing of the two oldest affected siblings was performed. Exome data was analyzed using the web-based application Ingenuity. Variants with a minor allele frequency of greater than 0.01%, or with low read quality, were filtered out, and heterozygous variants shared between the two affected siblings were identified. Genes of the variants that met the specified parameters were manually reviewed for relevance to neuromuscular development.

**Results:** Based on manual analysis, nine candidate genetic variants were identified based on their involvement in neuromuscular development and predicted pathogenesis.

**Next Steps:** Exome sequencing of the father and youngest two siblings will be completed to narrow the list of candidate genes. Validation of candidate variants will be pursued through gene sequencing, and cellular assays. Depending on the nature of the variant, it may be possible to demonstrate a damaging effect through assessment of gene expression levels, altered splicing, abnormal protein localization, or decreased protein production.

**Significance:** Determining the genetic cause of this family's congenital familial vocal cord paralysis and clubfoot may increase our understanding of the embryological development of these disorders. It will also allow for genotype-phenotype correlations that may improve care of affected children. Since this syndrome is rare in the literature, reporting the clinical features of this family will help to inform future physicians caring for similarly affected children.



**Macy Zou**, Undergraduate Student  
Supervisor(s): Lori Tucker

**Title:** Evaluating the clinical utility of measures of neurocognitive function in childhood-onset systemic lupus erythematosus

**Authors:** Macy Zou, David Cabral, Jaime Guzman, Kimberly Morishita, Kristin Houghton, Ross Petty, Hermine Brunner, Lori Tucker

### Abstract

**Background:** Neuropsychiatric Systemic Lupus Erythematosus (NPSLE) is a serious organ system manifestation in patients with SLE, and 43-95% of children with childhood-onset SLE (cSLE) reported having NPSLE. NPSLE may affect a patient's cognitive development, skill learning, and concentration abilities. Diagnosing and detecting NPSLE is difficult, and requires lengthy neuropsychiatric testing that is unavailable in rheumatology clinics. The Pediatric Automated Neuropsychological Assessment Metrics (PedANAM) is a computerized battery of tests developed for pediatric patients, and may be a practical and efficient screening method for monitoring and detecting neurocognitive changes in cSLE patients. Little has been described regarding interpretation of PedANAM scores, and how the results compare to other neurocognitive measures used with cSLE patients.

**Objective:** To examine the PedANAM scores of single centre cohort cSLE patients and compare the scores with other measures of neurocognitive function.

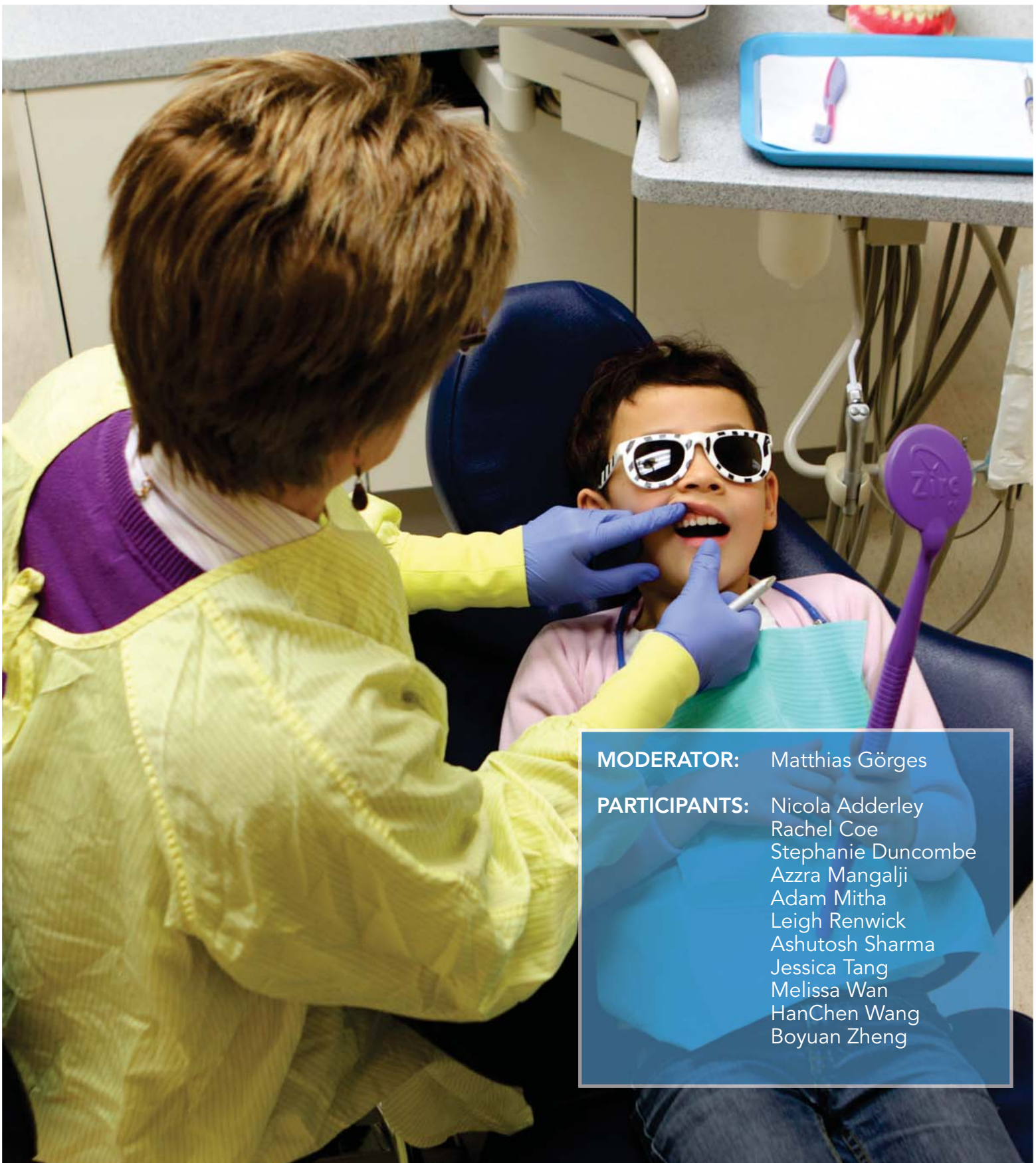
**Methods:** Participants were recruited in the Rheumatology clinic at BC Children's Hospital. At study entry and every 6 months, participants and parents completed the PedANAM test and the Pediatric Perceived Cognitive Function Questionnaire (PCF-43) respectively in clinic. The pediatric rheumatologist completed the American College of Rheumatology 19 NPSLE symptoms form (NPSLE-ACR) and the SLE Disease Activity Index 2000 (SLEDAI-2K). The PedANAM was scored using two different algorithms: PedANAM-CPSPCA and PedANAM-CPSMultiscore. Cut-off scores were determined to indicate need for further neuropsychiatric evaluation. Results of these scores were compared with the other measures using Pearson correlation and examined for trends.

**Results:** Total of 28 participants was enrolled and 95 visits completed. The PedANAM-CPSPCA and PedANAM-CPSMultiscore identified 13 and 5 patients respectively with scores suggesting further neuropsychiatric evaluation needed. The PCF-43 selected 4 patients with abnormal scores and the NPSLE-ACR identified 2 patients with neurocognitive dysfunction. Little correlation was found ( $r < 0.12$ ;  $p < 0.328$ ) between the measures. The SLEDAI-2K also had weak relationships with all 4 measures ( $r < 0.138$ ;  $p < 0.181$ ). No participant was identified by all 4 tests as needing further neuropsychiatric evaluation.

**Conclusions:** Based on the results, further studies are required to better understand the utility of PedANAM individually in clinical settings. The cut-off points for PedANAM-CPS, the ceiling effect of PCF-43, and proper training for answering NPSLE-ACR require further investigations.

# POSTER SESSION FIVE

CLINICAL



**MODERATOR:** Matthias Görge

**PARTICIPANTS:** Nicola Adderley  
Rachel Coe  
Stephanie Duncombe  
Azzra Mangalji  
Adam Mitha  
Leigh Renwick  
Ashutosh Sharma  
Jessica Tang  
Melissa Wan  
HanChen Wang  
Boyuan Zheng

**Nicola Adderley**, Undergraduate Student  
Supervisor(s): Harold Siden & Melissa Harvey

**Title:** Enhancing the quality of palliative care for children with cancer

**Authors:** Nicola Adderley, Melissa Harvey, Harold Siden, Adam Rapoport, Kimberly Widger

### Abstract

By alleviating physical, psychosocial, and emotional problems, palliative care for children aims to improve the quality of life of patients and families faced with severe illnesses that are not likely to be cured. Palliative care should be incorporated into a patient's care from diagnosis and throughout the disease course. Recent Canadian surveys indicate that referrals to palliative care teams are not made for many children who die from cancer, and when referrals are made they are shortly before death. Health professionals report receiving little pediatric palliative care training, which may contribute to complaints of sub-optimal care from families.

The national roll-out of the Education in Palliative and End-of-Life Care for Pediatrics (EPEC-Pediatrics) curriculum is designed to provide health professionals with knowledge and resources to improve access to palliative care. To measure the impact of EPEC-Pediatrics on oncology patient and family outcomes, quality indicator data will be collected before and after an 18 month intervention at 15 Canadian sites. Quality indicator data includes Parent/Child Surveys (Peds QL4.0; Memorial Symptom Assessment Scale; Survey About Caring for Children With Cancer; Quality of Children's End-of-Life Care Instrument), Bereaved Parent Surveys, and retrospective health record reviews. 'Pre'-test data collection occurred in the summer of 2015.

Due to data-sharing agreements, only the results of the retrospective review at BC Children's Hospital are presented. Of the 26 children who died from cancer between March 2014 and March 2015, 24 (92%) were referred to specialized palliative care teams. Only 5 (21%) of these children were referred within once month of diagnosis, and 1 (4%) child was referred in their final month of life. The median time between referral to palliative care and death was 143 days. The majority of patients passed away in hospices (62%), while others passed away at home (19%) or in hospital (19%).

These results provide a baseline for comparison following the roll-out of the EPEC-Pediatrics curriculum. While the palliative team was involved with almost all of the children who died from cancer, most referrals were made long after diagnosis. Earlier referral is recommended to ensure families are supported throughout the disease process.

**Rachel Coe**, Undergraduate Student

Supervisor(s): Jan Friedman, Clara van Karnebeek & Margaret McKinnon

**Title:** Importance of an accurate RASopathy diagnosis for malignancy management illustrated by a case study with splenomegaly due to a de novo CBL mutation

**Authors:** Rachel R Coe, Margaret L McKinnon, Maja Tarailo-Graovac, Colin J Ross, Wyeth W Wasserman, Jan M Friedman, Paul C Rogers, Clara D M van Karnebeek

### Abstract

**Background & Aims:** The RAS-MAPK pathway is an important signaling pathway that regulates cell division and differentiation throughout the body. Mutations in the pathway's genes cause an increasing number of related disorders called RASopathies, including Noonan syndrome, neurofibromatosis type 1, and Costello syndrome. Because these mutations can predispose to certain types of cancer, including juvenile myelomonocytic leukemia (JMML), accurate diagnosis of RASopathies is of utmost importance. Here we present an illustrative case of a 7-year-old boy with unexplained splenomegaly, ADHD, mild learning difficulties, easy bruising, mild thrombocytopenia, and subtle dysmorphic features.

**Methods & Results:** Extensive haematological testing including a bone marrow biopsy showed borderline megaloblastoid erythropoiesis and borderline fibrosis. Metabolic testing (including the TIDE protocol), karyotype and chromosomal microarray were unremarkable. The family was enrolled into the TIDEX study, and trio whole-exome sequencing with semi-automated bioinformatics identified a de novo heterozygous germline CBL mutation (p.Tyr371His, c.1111T>C), subsequently confirmed by Sanger sequencing of all family members. We performed a literature review and found that this specific mutation has been reported to cause Noonan-like CBL syndrome and has been strongly implicated in JMML after somatic loss of function of the wildtype allele.

**Discussion:** CBL is a tumour-suppressor gene in the RAS-MAPK pathway in which heterozygous germline mutations cause the RASopathy Noonan-like CBL syndrome. Our literature review showed that phenotypes related to this disorder include many of the same features as Noonan syndrome—including dysmorphic facial characteristics, developmental delay, short stature, and congenital heart defects—but the clinical variability in terms of number and severity of these symptoms is significant. We present this otherwise healthy child with Noonan-like CBL syndrome to highlight that splenomegaly may be a presenting feature in children with this condition and thus expand the phenotype. Early recognition and diagnosis of Noonan-like CBL syndrome and other RASopathies is essential for optimal management and outcomes for patients, including cancer screening and preventative care given that JMML can often be cured by hematopoietic stem cell transplant if performed in the early stages of the disease.



**Stephanie Duncombe**, Undergraduate Student  
Supervisor(s): Kevin Harris

**Title:** A systematic review and meta-analysis of blood pressure measurement techniques in children

**Authors:** Stephanie Duncombe, Christine Voss, Kevin Harris

### Abstract

Introduction: Mercury sphygmomanometers (HgS) have been considered the gold standard to measure blood pressure (BP). Aneroid sphygmomanometers (AnS) and automated oscillometric devices (OD) are mercury-free alternatives, the latter of which are now recommended for use in adults given their good inter-rater reliability. However, there is equipoise regarding the optimal mercury-free BP measurement technique in children. We conducted a systematic review and meta-analysis to determine the validity of OD and AnS compared to HgS in children.

Methods/Results: We searched electronic databases (Medline, Embase, CINAHL, Web of Science) using relevant medical subject headings and keywords, and the following inclusion criteria: 1) age 3-18 years; 2) BP measured by HgS and at least one other method (AnS or OD); 3) BP measurement on the arm. Duplicates were removed and titles/abstracts were reviewed by one author. Two authors then independently reviewed the remaining articles to determine inclusion. In case of disagreement, authors discussed articles to reach consensus. We extracted relevant data (n, mean and SD or mean difference) from articles and performed a meta-analysis (RevMan v.5.3) to determine the weighted mean difference [95%CI] between BP measurements obtained by HgS compared to AnS or OD. Of the initial 1415 articles, 92 articles underwent full text review. We included 29 studies of OD (18,250 children). Meta-analysis showed that SBP and DBP in the OD was higher (SBP: 3.05mmHg [2.85, 3.24], DBP: 2.43mmHg [2.24, 2.61]) than the HgS measurements. We only found 3 articles that compared AnS with HgS and therefore did not conduct a meta-analysis.

Conclusion: OD overestimates SBP in children by 3.1 mmHg and in DBP by 2.4 mmHg. The clinical importance of this difference in measurement warrants evaluation.

**Azzra Mangalji**, Undergraduate Student  
Supervisor(s): Shazhan Amed

Title: Quality of pediatric diabetes care

Authors: Azzra Mangalji, Shelly Keidar, Shazhan Amed

### Abstract

Background: Previous research has shown that of the ~2000 children (<20 years) in BC with type-1 diabetes (T1D), 54% are not receiving adequate health care as recommended by national and international Clinical Practice Guidelines (CPGs) (e.g. number of physician visits/year and screening tests for complications). This suboptimal adherence to CPGs may contribute to poor diabetes management in youth leading to greater risk for diabetes-related complications in adulthood. In this study, we aim to understand the individual (e.g. sex, age, emotional support) and health-system factors (e.g. distance to clinic, model of care) affecting diabetes self-management and influencing health outcomes. We also aim to identify barriers and facilitators to adhering to treatment recommendations in order to inform quality improvement initiatives.

### Study Objectives:

1. To identify individual and health-system factors influencing adherence to T1D management; and
2. To determine if adherence to the T1D CPGs is associated with health outcomes.

The objective of this project was to describe patients recruited into the study (thus far) in terms of their survey response rates, geographic representation and demographic features in order to inform future recruitment and ensure that a sample representative of BC is attained.

### Methods:

1. Patients were recruited from diabetes clinics across BC.
2. Validated surveys were administered to assess potential barriers and facilitators of adherence to care, and demographic characteristics of patients.
3. Data was collected from clinical charts (i.e. diabetes regimen, A1C, co-morbidities, etc).

Descriptive statistics (means, proportions, and frequencies) were used to describe recruitment rates, participants' demographic characteristics, and survey responses.

Results: Recruitment began in April 2015. Currently, 60 families have been recruited (survey response rate: 56.7%). While majority of respondents were from Vancouver Island and Vancouver Coastal Health Service Delivery Areas (HSDA), less than 10% of recruitment goals were reached in the Interior, Northern, and Fraser HSDA's. The average age of respondents was 12 years, majority (97.1%) of which were of Caucasian descent.

Conclusions: Recruitment efforts should be increased for patients from the Interior, Northern, and Fraser HSDA's, along with children of other ethnicities in order to obtain a sample representative of BC.

**Adam Mitha**, Undergraduate Student  
Supervisor(s): Lori Tucker

**Title:** LEAP: Linking exercise, activity and pathophysiology in juvenile idiopathic arthritis

**Authors:** Adam Mitha, Heather Macdonald, Heather MacKay, Lori Tucker

### Abstract

Juvenile idiopathic arthritis (JIA) is one of the most debilitating chronic diseases Canadian children face today, affecting an estimated 10,000 youth across the country. JIA is used to describe a group of conditions unified by chronic inflammatory joint disease. Physical activity (PA) and weight-bearing exercise are potential targets for intervention in light of current evidence that children with JIA engage in less PA and are less physically fit than their healthy peers.

This study aims to assess the effect of a 6-month home-based exercise program on clinical, bone, and muscle outcomes in youth with juvenile idiopathic arthritis (JIA). We hypothesize that participation in a home-based exercise program will improve clinical outcomes, lumbar spine bone mass and muscle strength and power in youth with JIA. Improvements in clinical outcomes and muscle strength and power will also be evident after 3 months of the exercise program.

We will use a pre-post study design to evaluate the efficacy of a home-based exercise program for improving clinical outcomes, bone mass and muscle strength in children with JIA. 30 children between the ages of 8 and 16 with JIA will be recruited from the Rheumatology Clinic at BC Children's Hospital for participation in the study. In addition to standard rheumatological care, study participants will participate in a tailored exercise regimen designed by an exercise specialist. This program will include a combination of resistance training (with Thera-Bands), hand-grip exercises and simple jumping exercises. Participants will record their adherence to the program in a logbook. Baseline measurements (Jan-Mar 2015) will include clinical outcomes (i.e. disease activity, overall well-being and function), quality of life, bone mass (lumbar spine areal bone mineral density by dual energy X-ray absorptiometry) and muscle strength and power (isokinetic testing; Biodex, jumping mechanography). We will repeat all measurements at 3- and 6-months, except bone mass which will only be reassessed at 6-months. We will use repeated measures analysis of variance to examine change in each outcome over time adjusting for important covariates (i.e. sex, maturation).



**Leigh Renwick**, Undergraduate Student  
Supervisor(s): Sheila Innis

**Title:** Toddler essential dietary fats and their role in learning and attention

**Authors:** Leigh Renwick, Sheila Innis, Julie Matheson

### Abstract

Background: Essential fatty acids cannot be synthesized by the body, and therefore must be consumed in the diet. Of importance to this study, the omega-3 ( $\omega$ -3) fatty acid, docosahexanoic acid (DHA), is essential to proper brain development and function. DHA is present in fatty fish, and is found in smaller quantities in meat, poultry, and eggs. DHA can also be derived from alpha-linolenic acid and eicosapentanoic acid precursors from the diet. Mother's breast milk is a rich source of DHA, but the transition from a high DHA diet to foods low in  $\omega$ -3/DHA after weaning may increase risk of DHA insufficiency in infants 18-24 months-of-age. Although DHA is the major fatty acid in the brain, the relationship between dietary DHA and childhood cognitive development is not well understood. Evidence shows that increased attention and decreased distractibility reflect maturation of frontal structures and pathways in the cortex; therefore, by using attention and distractibility tests, we are able to infer DHA status in the brain in order to draw comparisons between DHA supplement and placebo groups.

Objective: This study has two aims: (1) to determine whether current feeding practices among infants 18-24 months-of-age increase risk of DHA insufficiency and (2) to determine if DHA inadequacy affects brain development.

Hypotheses: We hypothesize that (1) dietary intakes of  $\omega$ -3/DHA will be inadequate in infants 12-24 months-of-age, and (2) brain development will be slowed or altered in infants 12-24 months with low  $\omega$ -3/DHA.

Methods: Study participants (n=133) at 12 months-of-age are randomly divided into DHA supplement or placebo groups for 12 months. Attention and distractibility are assessed at 18 and 24 months-of-age. For the purpose of the single object attention test, participants are given a toy for a period of 5 minutes, and the length of time they stay attentive and engaged with the toy is recorded and analyzed. Ability to attend to an object for a longer period of time suggests increased maturity of cortical structures and pathways.

Outcomes: This study is ongoing; data from multiple object attention tests as well as distractibility assessments will be analyzed to provide more comprehensive results.

**Ashutosh Sharma**, Undergraduate Student  
Supervisor(s): Kevin Harris

**Title:** Endocarditis rates in patients with bovine jugular vein conduits compared to other right ventricle to pulmonary artery conduits

**Authors:** Ashutosh Sharma, Anita Coté, Kevin Harris

### Abstract

Background: Patients requiring pulmonary valve replacement due to congenital heart disease (CHD) may have a right ventricle to pulmonary artery (RV-PA) conduit implanted for proper flow of blood. This implanted conduit may be a bioprosthetic valve made from another species or a homograft from a cadaver. Bovine jugular vein based conduits (BJV) have gained widespread acceptance due to their availability and strong hemodynamic outcomes. Recently, however, there has been an increasing number of small case series reporting infection of the soft tissue of the heart (infective endocarditis) associated with the use of BJV. The data from the cardiac interventional and surgical literature has not yet been systematically evaluated.

Methods: A systematic review was conducted. The literature search identified relevant articles from MEDLINE, EMBASE and CINAHL with the use of applicable search terms and subject headings. Studies were included in this review if they featured patients with CHD who had undergone RV-PA conduit placement and the following fields were reported: type of conduit placement, method of conduit placement, infective endocarditis (IE) incidence and the study follow-up time. A linear regression was used to assess the association between IE and follow-up time. Between-group differences in IE incidence were assessed via Mann-Whitney U tests.

Preliminary Results: 610 articles were compiled from the literature search following the removal of 270 duplicates. A further 434 articles were excluded based on a title and abstract screening, leaving 176 articles for full-text review. 33 articles were included in this preliminary analysis. It appears there is no association between follow-up time and IE incidence for BJV ( $n=15$ ,  $p=0.08$ ) and homografts ( $n=12$ ,  $p=0.09$ ). IE incidence was significantly higher in studies using BJV based conduits compared to homografts ( $n=27$ ,  $p=0.003$ ). There was no association between IE incidence in studies placing BJV surgically or through cardiac catheterization ( $n=15$ ,  $p=0.51$ ).

Conclusions: The increased IE incidence regarding BJV conduits reported in the literature may be not be due to the method of conduit placement, but rather the characteristics of the underlying BJV tissue. Future investigation of IE incidence in relation to valve types is warranted.

**Jessica Tang**, Undergraduate Student  
Supervisor(s): Kelly Brown

**Title:** CAN-Fever: A Canadian Patient Registry for children and youth with autoinflammatory disease

**Authors:** Jessica Tang, Kelly Brown, Lori Tucker

### Abstract

Autoinflammatory diseases are a relatively new collection of diseases first recognized 15-20 years ago. These diseases most often begin in childhood and are characterized by unprovoked, recurrent episodes of inflammation that occur every 2-8 weeks, with accompanying symptoms including joint swelling, skin rash, pain, abdominal pain, and other organ system findings. These diseases are rare, difficult to recognize, and often a diagnosis may be delayed for months to years during which time the child may be subject to multiple courses of unnecessary antibiotics and needless investigations. Although some patients have identified monogenic gene mutations, there is no known cause for the majority of affected patients.

Unlike initiatives that began many years ago in Europe and at the National Institutes of Health in the US, in Canada there are no specialized care centres or translational research programs in autoinflammatory diseases. Most clinicians have only limited access to genetic testing, and there are no consensus treatment guidelines, so children often receive no treatment or general immunosuppressive therapy. Some Canadian patients may go outside the country for expert consultation. The negative impact on children and their families is enormous.

CAN-Fever is the first national registry in Canada developed for children with autoinflammatory diseases and will be led by researchers at the BC Children's Hospital and CFRI. CAN-Fever will be based on European databases and will allow us to identify, track and house multi-centered, longitudinal clinical data and biological samples. CAN-Fever will allow us to improve our understanding of autoinflammatory diseases (e.g. epidemiologic trends, treatment responses, driving mechanisms, etc.) and ultimately lead to earlier identification and diagnosis, develop new measures to assess disease activity and develop evidence-based treatment guidelines to improve care for patients with autoinflammatory diseases.

**Melissa Wan**, Undergraduate Student  
Supervisor(s): Niranjan Kissoon

**Title:** Assessing the tropical disease knowledge needs in Canadian pediatric emergency medicine: A pilot study

**Authors:** Melissa Wan, Quynh Doan, Niranjan Kissoon

### Abstract

Background: In tropical and subtropical countries, travellers are exposed to high rates of infectious diseases that are non-endemic to Canada. With airline deregulation and the optimization of travel routes, the ease of international travel has never made the threat of imported tropical diseases so real. The emergency department is a common point of first contact with these diseases, and thus emergency physicians have a critical role in managing travellers who return with tropical diseases. Misdiagnosis and mismanagement may lead to prolonged illness, increased mortality, and spread to healthcare professionals and the community. Previous studies have reported a poor level of preparedness among general emergency physicians. However, knowledge to identify and manage a specific subset of tropical diseases in children and adolescents is necessary for those providing emergency care. To date, there has been no study assessing the knowledge of physicians practicing pediatric emergency medicine (PEM) concerning the common tropical diseases they are likely to encounter.

Objective: To create and validate a questionnaire in order to assess the knowledge of physicians practicing PEM in Canada in the area of tropical diseases.

Methods: A cross sectional questionnaire was created following a literature search and input from pediatric emergency physicians, global health specialists, and infectious disease specialists. The questionnaire will characterize the study population and their familiarity with tropical diseases, identify self-reported knowledge gaps, and evaluate the appropriateness of diagnosis and management of potential tropical disease cases using a 16-item case-based vignette section.

The questionnaire will be administered online following a modified version of the Total Design Method. A convenience sample of pediatric emergency physicians and infectious disease specialists at BC Children's Hospital (BCCH) will be used to assess the study procedure and the validity and reliability of the questionnaire.

Future directions and Relevance: Once the questionnaire has been validated it will be administered nationally to PEM physicians registered in the Pediatric Emergency Research Canada (PERC) database. The results of this questionnaire will yield valuable information to help develop continuing medical educational resources for physicians practicing PEM.

**HanChen Wang**, Undergraduate Student  
Supervisor(s): Millan Patel

**Title:** Is gastroschisis caused by a fetal infection?

**Authors:** HanChen Wang, Millan Patel, Patrick Tang, Ruth Miller

### Abstract

Backgrounds and Objective: Fetuses affected with gastroschisis have part or entire of their intestines sticking out of their abdominal area. Gastroschisis is lethal if untreated and affects the long-term health of the newborns. Current studies suggested that a few factors, principally young maternal age, associated with gastroschisis. However, no study investigated if an infectious agent causes this birth defect. Our project aimed to identify possible agents causing gastroschisis.

Approach: Traditional methods of identifying a disease-causing agent included repetitive work such as qPCR, culturing and serology. With advancements in massively parallel sequencing, supercomputing and bioinformatics, it is now possible to replace a test-by-test approach with a single test allowing comprehensive pathogen detection.

Hypothesis: An infectious agent causing gastroschisis will be present or found in significantly higher concentration in affected amniotic fluid (AF) than in control amniotic fluid.

Method: Our pipeline was designed to convert the collected maternal AF sample into pathogen identity statistics that could be viewed and analyzed by computer algorithm. After sequencing library construction, samples were sequenced using next generation chemistry on an Illumina HiSeq machine. The nucleotide sequences then underwent a modification process to remove low sequence quality regions. Since the project was designed to detect disease-causing agents, a filter in the pipeline removed human and duplicated sequences from the modified sequences. The pipeline then translated the remaining sequences into six reading frames and aligned them with the NCBI Non-Redundant database to determine the identities of these translated sequences. Metagenomics categorization assigned these sequence identities into branches of the phylogenetic tree and recorded the number of assigned sequences to each taxon. The results generated from this pipeline would allow comparisons in the numbers of sequences assigned to each taxon in the healthy and affected maternal AF sample. Agents found in affected AF samples and not in healthy AF sample would be proposed as potentially disease-causing and confirmed by other traditional methods.

Significance: This pipeline could define the metagenomics content of amniotic fluid and also develop a protocol for identifying infectious agents from cell-poor fluids that may cause human diseases.

**Boyuan Zheng**, Undergraduate Student  
Supervisor(s): Andrew Campbell

**Title:** Pediatric renal transplantation short-term outcome: The predictive value of perioperative variables

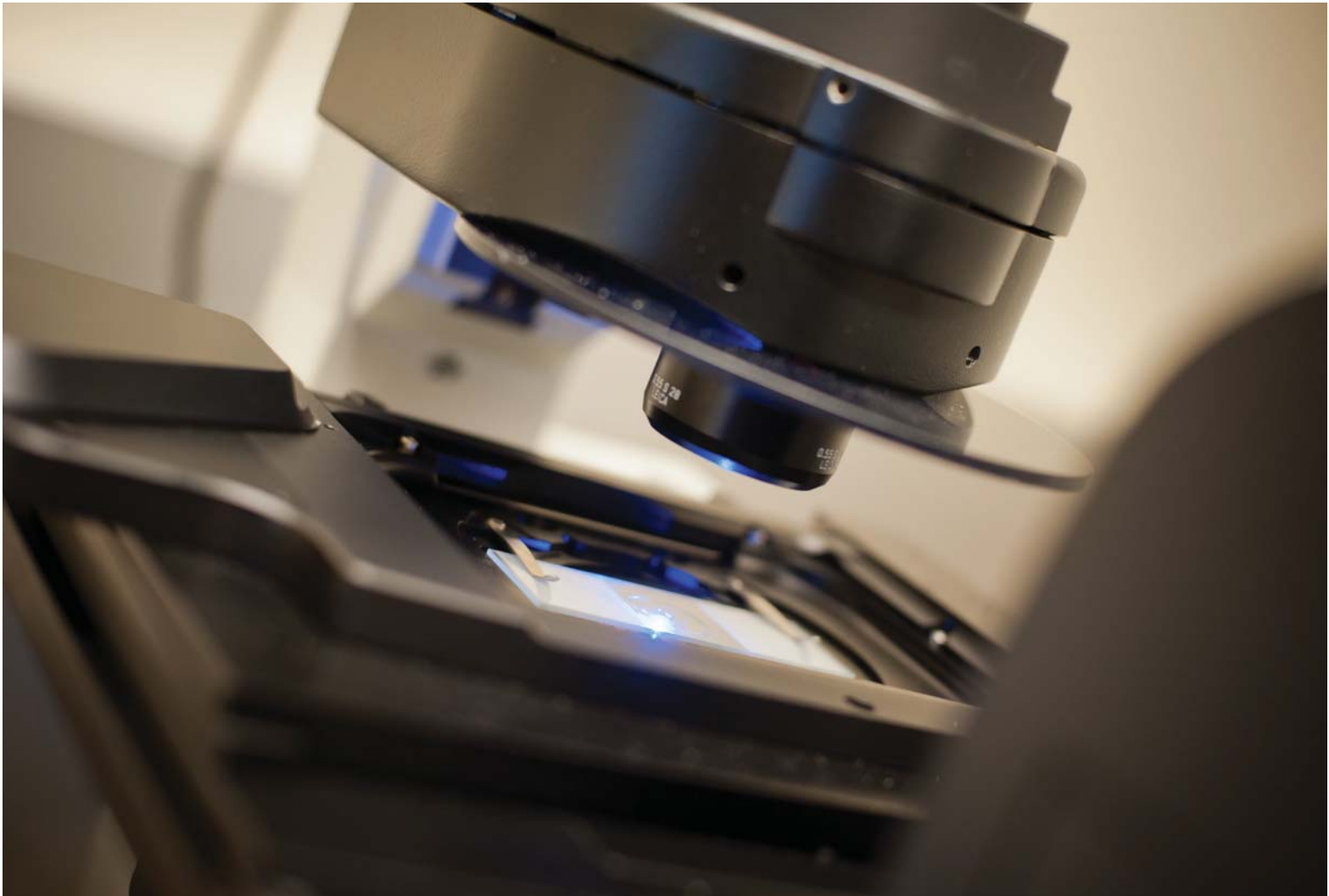
**Authors:** Zheng, Boyuan; Carreras, Erick M; Campbell, Andrew

#### Abstract

Chronic kidney diseases (CKD) in children are caused by a variety of medical conditions, such as congenital anomalies, nephrotic syndromes, and systematic diseases. Kidney transplantation is the current gold standard treatment for kidney failure or end-stage renal disease (ESRD). Many risk factors associated with renal graft outcome have been well studied by previous research. For example, short-term graft outcomes in children are influenced by cold and warm ischemic time, recipients' age at transplantation, and primary disease, among others. On the other hand, donor kidney characteristics, such as living versus cadaveric donor, donor's age, and comorbidities are better known to affect renal graft outcome in the adult population. Using these variables, an equation has been formulated to predict short-term renal graft outcome in adults, but not in children. Thus, the goal of this study is first to study the perioperative variables that influence graft outcome in children, and consequently, to construct a statistically derived predictive model for short-term graft outcome. A retrospective chart review was conducted. The study included all patients  $\leq 18$  years of age who had their first, and or only, renal transplantation between January 1st, 1992 and May 31st, 2013. A sample size of 142 (54.3% male, 45.7% female) participants resulted. Estimated glomerular filtration rate (eGFR) is our primary outcome at three time points: kidney transplant discharge date, and at 6 mos and 12 mos post-operatively. Our research team continues to conduct statistical analyses to both characterize and describe the data, as well as formulate the first predictive model of pediatric short-term renal graft outcome. The on-going analyses suggest that variables including source of donor, central venous pressure, and recipients' age of transplantation will have strong correlations with short-term renal graft failure. These results suggest that there is a method to delineate a predictive formula for renal graft outcome in terms of eGFR.

# POSTER SESSION SIX

BASIC SCIENCE/CLINICAL



**MODERATOR:** Andrew Tu

**PARTICIPANTS:** Cyrus Chehroudi  
Rozalyn Chok  
Mary Elrick  
Sang Hun Han  
Kushal Khera  
Daphne Y.D. Lu  
Mary Rose Pambid  
Dennis Wang  
Anqi Xiong  
Michael Xu



**Cyrus Chehroudi**, Medical Student  
Supervisor(s): Andrew MacNeily

**Title:** A survey of graduating pediatric surgical patients with neural tube defects: Towards developing an effective provincial model of care for transitioning patients in British Columbia

**Authors:** Cyrus Chehroudi, Damian Duffy, Ellen Lee, Bev Irwin, Andrew MacNeily

### Abstract

Introduction: Children with Spina Bifida (SB) typically have many chronic neuromuscular, urological, and gastrointestinal conditions and are cared for by a multi-disciplinary team at BC Children's Hospital (BCCH). Advances in surgical care have allowed these children to survive into adulthood. However, these patients subsequently must transfer into the adult healthcare system for long-term management. Adult healthcare providers often lack the specialized training required to manage transitioning patients' chronic conditions. These negative compounding factors in conjunction with parental aging often lead to neglected care after graduation. Therefore, we sought to determine the epidemiology, quality of life, and access to healthcare for adult SB patients in BC in order to assess the need for instituting new guidelines for improving care.

Methods: Adult graduates of the BCCH SB clinic were identified using the clinic database. Demographic and health status was updated by reviewing hospital records. Graduates will be mailed information on completing a transition questionnaire and a quality of life assessment tool specifically for SB, online or as mail-in surveys. These tools target patients' ability to handle healthcare needs independently, experiences with pediatric-to-adult transition and the resulting impact on health-related quality of life. Urologists known to care for adult SB patients will also be distributed surveys about their experiences treating these patients.

Results: Our review of the clinic database reveals 344 graduates in BC with a mean age of 29. The majority of graduates live in the Fraser Health Authority (41%), followed by Vancouver Coastal (22%), Interior-Health (16%), Island-Health (13%), and Northern-Health (8%). Twenty graduates expired over the last 30 years with the most common causes of death being ventriculo-peritoneal shunt failure and sepsis. The mean age of death was 27. Death occurred on average 7.6 years after graduation from BCCH. The percentage of deaths among total graduates was similar for all 5 health authorities (4-11%). We are awaiting survey responses from graduated SB patients and Urologists.

Conclusions: These data help characterize the demographics, outcomes and future outlook of adult SB patients in British Columbia, and will guide the development of future guidelines for effective transitional care.

**Rozalyn Chok**, Medical Student  
Supervisor(s): Caron Strahlendorf

**Title:** Pilot study to evaluate the feasibility of using virtual reality in the management of painful procedures

**Authors:** Rozalyn Chok, Caron Strahlendorf, Gillian Lauder

### Abstract

Children and adolescents with cancer routinely undergo painful procedures as part of their management and treatment. These pediatric patients and their families report that procedure-related pain is one of the most distressing aspects of the cancer experience. The physiological and psychological responses to pain not only directly affect children's health, but may also predispose pediatric cancer survivors to developing chronic pain in adulthood.

Good-quality pain management is essential in promoting functional recovery, improving long-term functional outcomes, and enhancing patient and family satisfaction. In the Hematology/Oncology/Bone Marrow Transplantation Clinic at BC Children's Hospital (BCCH), standard practice for procedures such as inserting an IV or accessing a venous access device (VAD) includes topical anesthetic cream as well as parental, auditory, or visual distraction techniques such as bubbles, stories, or iPads. Unfortunately, none of these techniques are completely effective in alleviating a child's distress.

In addition to standard practice techniques, virtual reality (VR) intervention could potentially achieve further reductions in pain and anxiety in pediatric patients. VR is a computer-graphic technology that immerses the user in a virtual environment. Recently, VR has been studied as a non-pharmacological analgesic and distraction tool. In previous studies involving children and adolescents, VR has consistently been shown to decrease patient distress, pain, and perceived time spent during medical procedures. However, no previous studies have investigated whether it is feasible to offer VR as part of routine pain management in the pediatric hematology/oncology clinic, which is what we hope to determine in our study.

In this pilot study, we will specifically evaluate whether the VR technology and apparatus are well-liked, well-tolerated, and practical for routine use in pediatric patients in the BCCH Hematology/Oncology/Bone Marrow Transplantation Clinic. We will recruit 30 participants (age 7-15) undergoing a needle-related procedure that does not require general anesthetic. Participants will wear a hands-free VR headset before and during their procedure and will answer questions about their pain, nausea, and overall experience immediately following the procedure. We hypothesize that our findings will reflect potential for incorporating VR into standard pain management practice for children requiring invasive procedures at BCCH.

**Mary Elrick**, Medical Student  
Supervisor(s): Marie-France Delisle

**Title:** The BC Fetal Anemia Registry: Improving province-wide surveillance and management of pregnancies complicated by alloimmunization and acute Parvovirus B19 infection

**Authors:** MA Elrick, WK MacDonald, MF Delisle

### Abstract

Fetal anemia has potential serious complications, including hydrops fetalis, and is a rare clinical event that requires surveillance and management by Maternal Fetal Medicine specialists at BC Women's Hospital. The most common causes of fetal anemia are red cell antigen alloimmunization and acute Parvovirus B19 infection, which have an estimated incidence of 2 per 10,000 pregnancies, equating to approximately ten cases annually in BC.

Historically, antenatal surveillance of pregnancies at risk of fetal anemia was performed by serial amniocenteses to measure bilirubin, a product of lysed red cells, in amniotic fluid. Now, non-invasive screening for fetal anemia using serial ultrasound measurements of middle cerebral artery peak systolic velocity is the standard of care. Fetuses suspected to be at risk of anemia undergo cordocentesis, hemoglobin testing and intrauterine blood transfusions if required. This management approach results in survival rates greater than 90%. To achieve optimal outcomes using these techniques, further research can help determine the optimal frequency of ultrasound monitoring, as well as indications and best practices for intrauterine transfusions.

It is challenging to streamline and optimize clinical practice for these pregnancies since fetal anemia cases are rare. Recognizing this, the British Columbia Fetal Anemia Registry was developed to collect data retrospectively and prospectively, as an essential tool for fetal anemia research. The database was developed using REDCap software and will collect detailed information about fetal anemia cases from January 2000 onward. Components of the database include: 1) maternal demographics, 2) Parvovirus B19 serology and red cell antibody titres, 3) genetics relevant to red cell antigen inheritance, 4) fetal blood typing techniques, 5) surveillance using amniocentesis and ultrasound, 6) technical details about intrauterine transfusion interventions, and 6) fetal and neonatal outcomes. Importantly, the British Columbia Fetal Anemia Registry will open opportunities for national fetal anemia studies, as it has been developed to be compatible with a similar database at the University of Toronto. Overall, our hope is that this database will improve the standard of care for pregnancies affected by fetal anemia while improving maternal and neonatal health outcomes.

**Sang Hun Han**, Medical Student  
Supervisor(s): Evelyn Stewart

**Title:** Prevalence and correlates of PANS/PANDAS cases within pediatric OCD

**Authors:** Sang Hun Han, Katherine McKenney, Annie Simpson, Andrea Boyle, Elaine Chan, Rhonda Ellwyn, S Evelyn Stewart

### Abstract

**Background:** Obsessive-Compulsive Disorder (OCD) is a common neuropsychiatric condition that affects 1-3% of the general population. In recent years, new terms have arisen to define putative subtypes or conditions presenting with pediatric acute-onset OCD, including Pediatric Acute-onset Neuropsychiatric Syndrome (PANS), and Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections (PANDAS).

**Objective:** Since prevalence rates and characteristics of PANS and PANDAS remain incompletely understood, this study was carried out 1) to assess prevalence of those meeting criteria for PANS/PANDAS in a clinical pediatric OCD population and 2) to study relevant clinical correlates between non-PANS/PANDAS and PANS/PANDAS OCD cases.

**Methods:** Patients from BC Children's Hospital Pediatric OCD Program were recruited to participate in the Registry Study and were initially assessed at baseline by a team of clinicians, including psychologists and psychiatrists. Clinician and self-report measures included OCD Background/Medical Questionnaire, OCD Family Function Scale, Anxiety Disorders Interview Schedule, and Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS).

**Results:** Only participants diagnosed with lifetime OCD at initial assessment (n=133) were included for analysis. Within this subset, 3.76% met criteria for PANS and/or PANDAS (n=5)--2 with PANS, 2 with PANDAS and 1 with both PANS and PANDAS criteria fulfilled. Those meeting PANS/PANDAS criteria were 40 times more likely to have a comorbid autoimmune disease (p=0.006) and two times less likely to report symptoms within the OCD factor containing symmetry, ordering, counting, checking and repeating (p=0.032). Furthermore, there was a tendency towards younger age at assessment (mean age=10.60; 13.10; p=0.053).

**Conclusion:** PANS and PANDAS presentations represented a small yet significant proportion of our clinical pediatric OCD population. Our findings indicate that PANS/PANDAS cases are more likely to present in the context of known autoimmune diseases, suggesting that they may be more susceptible to this type of presentation of pediatric OCD. Limitations include the relatively small sample size of those meeting PANS/PANDAS criteria and limited ability to do detailed comparative analyses. For future directions, comparative studies of pediatric autoimmune population and healthy controls to examine rates of PANS/PANDAS will be useful.

**Kushal Khera**, Medical Student  
Supervisor(s): Kishore Mulpuri

**Title:** Publication outcomes of abstracts presented at the 2009-2013 Pediatric Orthopaedic Society of North America (POSNA) annual meetings: Awarded vs. non-awarded abstracts

**Authors:** Kushal Khera, Emily Schaeffer, Kishore Mulpuri

### Abstract

Purpose: The Pediatric Orthopaedic Society of North America (POSNA) is dedicated to improving the quality of care and outcomes for children with musculoskeletal conditions. At each POSNA Annual Meeting, awards are given to selected Basic Science, Clinical Scientific, Paper Poster, and E-Poster abstracts. The purpose of the study was to determine publication outcomes of abstracts presented at the 2009-2013 POSNA annual meetings to examine the efficacy of the award process. This study compares mean impact factors, publication rates, and citation counts between awarded and non-awarded abstracts.

Methods: All abstracts from podium, poster, and e-poster presentations published in the 2009-2013 POSNA meeting programs were identified. PubMed, MEDLINE and Google Scholar were searched using the full abstract title to determine publication in a peer-reviewed journal. If the abstract was not found, the presenting author's name was searched along with keywords from the abstract title, to allow for alterations to the abstract title from presentation to publication.

Results: Of the 1055 abstracts presented at the 2009-2013 POSNA annual meetings, 55.9% (n=590) had been published in a peer-reviewed journal by June 2015. The data was divided into two groups: awarded (n=69) and non-awarded abstracts (n=986). The publication rate for awarded and non-awarded abstracts were 66.7% and 55.2% respectively ( $p=0.063$ ). Awarded abstracts had a significantly higher mean impact factor than non-awarded abstracts (3.29 vs. 2.15,  $p=0.0025$ ). Awarded abstracts had a shorter time to publication than non-awarded abstracts (12.3 months. vs. 17.0 months,  $p=0.02362$ ). The average number of citations for awarded and non-awarded abstracts was 13 and 9 respectively ( $p=0.06543$ ).

Conclusion: While there was no statistically significant difference in publication rate, awarded abstracts were more likely to be published in a higher impact factor journal with a shorter time to publication than non-awarded abstracts. No statistically significant difference was found in the number of citations.

Significance: The statistically significant difference in impact factor and time to publication give validity and merit to the awards process at POSNA annual meetings. However, the similarity in overall publication rates suggests that not receiving an award should not impede authors aiming to publish their work in a peer-reviewed journal.

**Daphne Y.D. Lu**, Medical Student  
Supervisor(s): Neil Chadha

**Title:** Prevalence and detection of abnormally shaped ears in newborns

**Authors:** Daphne Lu, Julie Pauwels, Lisa Jin, Frederick Kozak, Neil K. Chadha

### Abstract

Background: Many children are born with abnormally shaped ears but the prevalence of these abnormalities remains unclear with reports ranging from 1.7-55% and numbers vary widely among ethnic groups. This study is the first to investigate the prevalence and ethnic variation of abnormally shaped ears in the newborn population at BC Women's Hospital.

While the majority of abnormally shaped ears are benign, they can cause significant issues with self-esteem and bullying. Molding with soft splints or tape can resolve these abnormalities and avoid the need for future corrective surgery. However, newborns with these abnormalities are rarely identified and treated within the first few days of life, a time window when molding is most effective. In this study, we investigate whether a trained non-specialist can correctly identify ear abnormalities in newborns. This could provide a cost-effective means of ensuring that these children's health care needs are met in a timely fashion.

Method: The non-specialist (first year medical student) was trained for 2 hours by an Ear Nose Throat (ENT) Specialist on normal and abnormal ear anatomy using photographs and descriptions. Newborns were recruited from the maternity wards at BC Women's hospital and basic demographic information including the newborn's age and ethnicity was collected. Each of the newborn's ears was photographed and two ENT specialists as well as the trained non-specialist analyzed photographs. Each ear was deemed normal or abnormal, along with the type of abnormality. Inter-rater agreement was analyzed.

Results: Preliminary results based on 120 participants enrolled in the study show that a non-specialist detects abnormally shaped ears with a sensitivity of 98.8% and specificity of 87.5%.

Summary: Our study illustrates the potential for a non-specialist to accurately detect newborn ear abnormalities. We hope to recruit 500 subjects by the end of the summer, allowing us to accurately assess the prevalence and ethnic variation of abnormally shaped ears of newborns at BC Women's Hospital.

**Mary Rose Pambid**, Medical Student  
Supervisor(s): Rod Rassekh

**Title:** Continuous infusion ondansetron for the management of nausea & vomiting in patients receiving cisplatin

**Authors:** Mary Rose Pambid, Björn Baadjes, James E. Potts, Roberta Esau, Rod Rassekh

**Abstract**

Despite advances in anti-emetics, acute chemotherapy-induced nausea and vomiting (CINV) continues to decrease the quality of life in children with cancer. The current standard of care for patients treated with the chemotherapy cisplatin, a highly emetogenic agent, is to administer ondansetron as a bolus infusion to counter CINV.

Ondansetron is a 5-HT<sub>3</sub> (serotonin) antagonist which inhibits signaling to the vomiting center in the brain and has minimal side effects. It is administered as a bolus infusion, but some patients do not respond to this treatment. At BC Children's Hospital, continuous infusion of ondansetron in those failing bolus therapy has become standard practice for several years. Thus, it is imperative to evaluate its efficacy given this different method of administration. Our retrospective study consists of n=101 charts of patients who have received cisplatin and ondansetron. Our preliminary results demonstrate an improvement in emesis prevention when using continuous infusion compared to bolus alone.



**Dennis Wang**, Medical Student  
Supervisor(s): Megan Levings

**Title:** The role of chemokine production by T regulatory cells in autoimmunity

**Authors:** Dennis Wang, Anne M Pesenacker, Megan K Levings

### Abstract

Regulatory T cells (Tregs) are characterized by expression of FOXP3 and have an important role in controlling immune homeostasis and stopping autoimmunity by suppressing effector cells. Tregs need to be in close proximity to enforce their effects. We have reported that Tregs can secrete chemokines, molecules which drive cell migration. We hypothesize that Tregs secrete chemokines to attract effector cells, bringing them closer to suppress them. Additionally, co-stimulatory and co-inhibitory receptors expressed on Tregs may influence chemokine production. This project aims to examine how co-stimulatory and co-inhibitory molecules affect Treg and conventional T cell (Tconv) phenotype, as well as the chemokines they produce. 11-colour flow cytometry is used to assess the expression of several co-stimulatory molecules such as ICOS, CD226, CD161 and SLAM, co-inhibitory molecules such as TIGIT, CD96, and CD244, and Treg functional molecules such as CTLA4, LAP, GARP, FOXP3 and CD25, as well as the expression of their ligands such as SLAM, CD155 and CD112. Tregs and Tconv are stimulated under various conditions, and the chemokines they produce are analyzed by chemokine bead assay (CBA). All experiments are performed with immune cells isolated from healthy patients and patients with autoimmune disease, allowing for the comparison of Tregs in normal and autoimmune conditions. We found that 70% of FOXP3+ cells express ICOS and 41% of FOXP3+ cells express CTLA4. A large proportion of FOXP3+ Tregs express TIGIT, with an average of 57% TIGIT+CD226+, 18% TIGIT+CD226- and 21% TIGIT-CD226+ cells. 3% of FOXP3+ cells express CD120b with constitute low expression of CD120a. At the site of inflammation in autoimmune arthritis, these receptors are expressed at higher levels.. CD14+ monocytes express high levels of CD155 and CD112, whereas CD4+ T cells and CD19+ B cells did not express CD155 or CD112. Tregs that express these receptors might interact with immune cells that present the respective ligands. Therefore, the multiple receptors on Tregs and the ligands on other immune cells might modulate the pathways affecting chemokine production by Tregs. CBA of supernatants from Tregs stimulated under various conditions will establish the importance of these co-stimulatory and co-inhibitory molecules for Treg derived chemokines.

**Anqi Xiong**, Medical Student  
Supervisor(s): Wendy Norman

**Title:** The Canadian Sexual Health Survey: Contraception access research team

**Authors:** Anqi Xiong, Wendy Norman

### Abstract

Background and Objectives: By the age of 45, 31% of women in Canada have had an abortion. Unlike several other Western countries, Canada does not provide subsidy for women accessing efficacious contraceptive methods. In BC, it is estimated that 15,000 abortions are performed annually. The BC Provincial Health Officer has highlighted the need to improve access to contraception as a key health priority. In order to advocate and support the development of relevant health policies, high quality data need to be collected on currently unknown determinants of Canadian sexual and reproductive health with considerations of cultural and socioeconomic context. We developed the Canadian Sexual Health Survey (CSHS) is to assess and measure these parameters and apply them to devise cost-effective policy options.

Methods: The survey contains validated questions from seven international sexual health surveys and was pilot tested last summer. This survey employs multi-stage cluster sampling and stratifies households in BC by Provincial Health Authorities and income. Women under 30 years of age or in low socioeconomic regions are overrepresented. The survey is currently conducted as a door-to-door, computer-assisted, personal interview with a confidential-audio self-entry portion in English and Mandarin Chinese. We aims to collect 75 surveys in each local health region or 3000 surveys total amongst females aged 14-49.

Results and Discussion: We have completed survey collection in 9 local health regions and 11 locations are underway. Over 1000 surveys have been obtained. Key themes cover history of contraceptive use, including adherence and prevalence, pregnancy outcomes and intentions, and social determinants of health. Evidence based on this data will help to construct Canada's first Contraception Economic Model, which will enable trials of alternative policies for contraception subsidy in Canada.

**Michael Xu**, Medical Student  
Supervisor(s): Quynh Doan

**Title:** Evaluating the burden of Outpatient Parenteral Antimicrobial Therapy (OPAT) on BC Children's Hospital emergency department utilisation

**Authors:** Michael Xu, Quynh Doan

### Abstract

Background and Rationale: Returns to emergency department (RTED) occur when patients make multiple visits to the emergency department (ED) following initial discharge for a related clinical complaint. Literature report RTEDs within 72 hours of initial visit to pediatric EDs (PED) vary between 2-5% of total visits. For health systems, RTEDs pose significant logistical and economic challenges. Although sometimes appropriate, RTEDs may be unwarranted when patients' medical condition and treatment plan are critically examined.

Currently, patients at the BCCH ED receiving outpatient parenteral antimicrobial therapy (OPAT) require multiple arranged RTED for therapy. While there is wide practice pattern variability regarding the route of antibiotic administration, there is growing evidence that for most uncomplicated pediatric infections such as cellulitis, pneumonia and urinary tract infections (UTIs), antibiotics are as effective given orally as intravenously. It is therefore important to critically examine local OPAT practices at BCCH to understand the burden that OPAT poses on ED utilisation.

Methods: We conducted a single-centre retrospective cohort study using administrative database and chart review at the BCCH PED between May 1 2012 to April 30 2013. The goal was to characterize OPAT usage among scheduled RTED within 7 days after index visit. Our primary objective was to measure the proportion of scheduled RTEDs for which OPAT was given. Our secondary objective was to cross-examine OPAT cases against current clinical guidelines for three clinical diagnoses: cellulitis, pneumonia, and UTIs and estimate the proportion of preventable RTEDs for OPAT had best practice guidelines been used.

Results: We identified 1045/1323 (79%) scheduled RTED visits for OPAT, representing 2.6% of total



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