University of Manitoba

the Children's Hospital Research Institute of Manitoba
a division of the Children's Hospital Foundation of Manitoba

DREAM

Diabetes Research Envisioned and Accomplished in Manitoba

Presents

The 5th Annual Diabetes Research Symposium on:

The Emerging Science of Big Data:

Using '-omics' approaches & large datasets in diabetes and health research

Wed. November 9th – Thurs. November 10th, 2016

Wednesday November 9th, 2016

9:00am – 1:00pm	**Poster Setup, self-registration** (Pick up name badge and program from registration table) *Joe Doupe Concourse – 2nd Floor BMSB*
12:00pm – 1:00pm	**Special CIHR announcement and Media Event** *John Buhler Research Centre – Room 500 (5Th Floor)*
1:00pm – 3:00pm	**Poster Competition & Lunch** – Preliminary Round *(Winners to present in Guided Poster Session Thursday at 4pm)* *Joe Doupe Concourse – 2nd Floor BMSB* Note to Poster Presenters, please be at your posters at the following times: 1:30pm – 2:00pm: Even poster numbers 2:00pm – 2:30pm: Odd poster numbers
3:00pm – 4:30pm	**DREAM Diabetes Research Group Showcase** *Theatre C – 2nd floor BMSB*
3:00pm – 3:10pm	Opening remarks (*DREAM Co-Directors: Drs. Jon McGavock & Grant Hatch*)
3:10pm – 3:20pm	**Dr. Elizabeth Sellers:** *"The History of Type 2 Diabetes in Youth in Manitoba"*
3:30pm – 3:30pm	**Dr. Brandy Wicklow:** *"The Next Generation: Lessons learned from a Manitoba birth cohort"*
3:30pm – 3:40pm	**Dr. Allison Dart:** *"iCARE - improving renal Complications in Adolescents with type 2 diabetes through REsearch: A cohort study"*
3:40pm – 4:00pm	**Dr. Vern Dolinsky:** *"Translational research into the developmental origins of metabolic disorders"*
4:00pm – 4:10pm	**Dr. Paul Fernyhough:** *"Drug therapy for diabetic neuropathy"*
4:10pm – 4:20pm	**Dr. Jon McGavock:** "Creating networks for the treatment and prevention of diabetes in youth"
4:20pm – 4:30pm	Closing Discussion Period
4:30pm – 5:30pm	**"Pathways to your DREAM job"** Career Development Panel Discussion *Theatre C – 2nd floor BMSB* Panelists: ***Dr. Silva Arslanian, MD*** • Pediatric Endocrinologist, Children's Hospital of Pittsburgh • Director, Pediatric Clinical and Translational Research Centre • Director, Pediatric Weight Management and Wellness Centre • Professor, Pediatrics; Clinical and Translational Science Institute, University of Pittsburgh School of Medicine ***Dr. Gillian Booth, MD*** • Endocrinologist • Scientist, Li Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto • Associate Professor, Medicine; Institute of Health Policy, Management and Evaluations, University of Toronto • Adjunct Scientist, Institute for Clinical and Evaluative Services, University of Toronto ***Dr. Michael Kobor, PhD*** • Professor, Medical Genetics, University of British Columbia • Scientist, Child and Family Research Institute, BC Children's Hospital • Scientist, Centre for Molecular Medicine and Therapeutics • Tier 1 Canada Research Chair in Social Epigenetics ***Dr. Jim Johnson, PhD*** • Professor, Cellular and Physiological Sciences; Surgery, University of British Columbia • Leader, Diabetes Research Group, Life Sciences Institute, University of British Columbia • Editor-in-Chief, Islets
7:00pm – 11:00pm	***"DREAM-Eve"* Networking Mixer** *(Hosted by CON-SNP Manitoba)* Clementine*, 123 Princess Street*

Thursday November 10th, 2016

Pediatric Grand Rounds: *Theatre B* *Chair: Dr. Elizabeth Sellers*	
8:00am – 9:00am	3rd ***Annual Dr. Heather Dean Lecture*** **KEYNOTE: Dr. Sylva Arslanian,** *Children's Hospital of Pittsburgh* ***"Youth Type 2 Diabetes: Tribulations of an Epic Love Story"***
9:00am – 9:15am	**iCare Patient Advisory Group Video Presentation**
9:15am – 9:45am	Coffee, light breakfast, registration, poster set-up - *Joe Doupe Concourse – 2nd Floor BMSB*
Morning Session: *Theatre B* *Chair: Dr. Vernon Dolinsky*	
9:45am – 10:00am	Opening remarks, Drum Ceremony and Indigenous Elder Opening Prayer
10:00am – 11:00am	**KEYNOTE: Dr. Michael Kobor,** *University of British Columbia* ***"Epigenetics in Human Health and Disease"***
11:00am – 11:15am	**Dr. Vikram Bhatia** – Next Generation Sequencing Platform (PI: Dr. Jim Davie) **Ubiquitin Carboxyl-Terminal Esterase L1 genomic location and function**
11:15am – 11:30am	**Anita Durksen** – iCARE Research Group (PI: Dr. Allison Dart) **Objective Measures of Mental Health and Distress in Manitoba Youth Living With & Without Type 2 Diabetes**
11:30am – 12:30pm	Lunch - *Joe Doupe Concourse – 2nd Floor BMSB*
Afternoon Session 1: *Theatre B* *Chair: Dr. Grant Hatch*	
12:30pm – 1:30pm	**KEYNOTE: Dr. James Johnson,** *University of British Columbia* ***"Excess Insulin Drives Obesity, Insulin Resistance and Lifespan Shortening"***
1:30pm – 1:45pm	**Dr. Laura Cole** – DREAM Research Group (PI: Dr. Grant Hatch) **Impaired Cardiolipin Biosynthesis Prevents Hepatic Steatosis and Diet-Induced Obesity**
1:45pm – 2:00pm	**Dr. Mohammad G. Sabbir** – St. Boniface Albrechtsen Research Centre (PI: Dr. Paul Fernyhough) **Novel therapy for diabetic neuropathy: studies on muscarinic acetylcholine receptor type-1 modulation of mitochondrial function via calcium/calmodulin-dependent protein kinase kinase β.**
2:00pm – 2:30pm	Coffee Break - *Joe Doupe Concourse – 2nd Floor BMSB*
Afternoon Session 2: *Theatre B* *Chair: Dr. Jon McGavock*	
2:30pm – 3:30pm	**KEYNOTE: Dr. Gillian Booth,** *University of Toronto* ***"Healthy Cities, Healthier Lives: Urban environments and risk of diabetes"***
3:30pm – 3:45pm	**Lisa Chu** – Child Health & Exercise Medicine Program, McMaster University (PI: Dr. B. Timmons) **Effect of 7 days of exercise on metabolic flexibility in children with obesity**
3:45pm – 4:00pm	**Allison Feely** – DREAM Research Group (PI: Dr. Jonathan McGavock) **Prevalence and Determinants of Dysglycemia in Youth in Canada**
4:00pm – 6:00pm	**Reception and Guided Poster Session (Poster Competition finalists to present)** Top 3 winners of Poster Session on Wednesday will present a second time in the guided poster session **winning presenters will be notified by email immediately after the poster session on Wednesday* 4:15pm – 4:25pm *Speaker #1 TBD* 4:25pm – 4:35pm *Speaker #2 TBD* 4:35pm – 4:45pm *Speaker #3 TBD*

WELCOME!

GREETINGS FROM THE CHRIM SCIENTIFIC DIRECTOR

Welcome to the 5th Annual DREAM Diabetes Research Symposium!

The DREAM Diabetes Symposium has quickly become a key event for researchers, medical professionals, trainees and others to learn the latest on diabetes research taking place here in Manitoba and around the world. Every year, the DREAM symposium continues to evolve and grow. In addition to presentations from world-renowned keynote speakers, the DREAM symposium offers a forum for our trainees to share their work with the wider Manitoban community. This year, the organizers received 32 abstracts for poster presentations, 6 of which were selected by the organizing committee to present their work to you today in a short-talk. Additionally, the symposium will kick off with the 3rd annual *Heather Dean Lecture in Excellence in Diabetes* where we will hear a presentation by Dr. Silva Arslanian from the Pittsburgh University School of Medicine. Enjoy the day and knowledge sharing as we continue to conduct research that will improve the lives of young people with type 2 diabetes.

Terry Klassen, MD
CEO and Scientific Director
CHRIM

GREETINGS FROM THE DREAM CO-DIRECTORS

We would like to welcome you to the 5th Annual Diabetes Research Envisioned and Accomplished in Manitoba (DREAM) Symposium. The 5th Annual Symposium will focus on Big Data- from omics to administrative data, and how these can improve the lives of persons living with diabetes through innovative discoveries. We are pleased to have an outstanding group of international and national keynote speakers that span the continuum of research from basic discoveries to clinical investigation and population health research. For the second year in a row, we will be highlighting the frontline work of our trainees within DREAM and those across the province and Canada that relate to diabetes research in children and adolescents. This year also marks a major milestone for DREAM as we secured two large team grants to expand our reach across the country. Take time Wednesday and Thursday to celebrate these successes with leaders from CIHR Institutes of Nutrition Metabolism and Diabetes; Aboriginal Peoples Health, Population and Public Health and Musculoskeletal Health and Arthritis.

Once again we are excited to bring together both basic and clinical research scientists in an intimate forum to discuss the most recent and relevant developments in these areas. We hope that you will enjoy this symposium and that you will come away with a new appreciation of the forms of community- and patient-oriented research that are currently underway in the realm of diabetes and the key role of Big Data in this field.

Jon McGavock and Grant Hatch
Co-Directors, DREAM

DR. HEATHER DEAN LECTURE

IN EXCELLENCE IN DIABETES

The 5th Annual DREAM Symposium marks the 3rd Annual Dr. Heather Dean Lecture in Excellence in Diabetes. This lecture was named in honour of one of the University of Manitoba's most recognized and trailblazing clinician scientists. Dr. Dean has been a pillar in several communities in our beloved province for nearly 40 years, including but not limited to the medical community, the pediatrics and child health community, the farming community, the sporting community and most famously, the knitting community. Dr. Dean has inspired countless trainees, patients, families and athletes during her tenure in the province. The DREAM team thought it was important to name the opening lecture for our symposium in Dr. Dean's name as without her dedicated commitment to diabetes in children and vision for team-based care, the DREAM team would not exist. The Annual Dr. Heather Dean Lecture in Excellence in Diabetes will symbolize the excellence in clinical care, research and interdisciplinary collaboration in the area of pediatric endocrinology that Dr. Dean has embodied and cultivated in the province of Manitoba. We hope that the lecture will also serve as an annual source of inspiration for young hearts and minds in the same way that Dr. Dean has inspired us over the past 30 years.

SPEAKER

DR. SILVA ARSLANIAN, MD

Youth Type 2 Diabetes: Tribulations of an Epic Love Story

Dr. Heather Dean and her team were pioneers in alarming the scientific community about youth type 2 diabetes more than three decades ago. Since then major scientific advances were made in the pathophysiology, management, and the complications of the disease. This lecture will discuss the pathophysiology of youth Type 2 diabetes, a rational for therapeutic interventions, the outcome of major clinical trials such as TODAY (Treatment Option for Type 2 Diabetes in Adolescents and Youth) and disease complications where the Winnipeg investigators have made major contributions. Lastly, there will be presentation about the stark contrast between youth and adult type 2 diabetes.

BIOGRAPHY

Silva Arslanian, M.D., is Professor of Pediatrics and Clinical and Translational Sciences at the University of Pittsburgh, School of Medicine. She is a pediatric endocrinologist and holds the Richard L. Day Endowed Chair in Pediatrics, at the Children's Hospital of Pittsburgh of UPMC. She is the Director of the National Institutes of Health (NIH)-funded Pediatric Clinical and Translational Research Center at the Children's Hospital of Pittsburgh and the Founding Director of the Weight Management & Wellness Center. Dr. Arslanian obtained her medical degree from the American University of Beirut and completed her pediatric residency training at the same institution. She completed her fellowship in Pediatric Endocrinology, Metabolism and Diabetes Mellitus at the Children's Hospital of Pittsburgh, USA. Dr. Arslanian's research focus is insulin resistance and pancreatic beta cell function during childhood growth and development in health and disease (obesity, pre diabetes, Type 2 diabetes, type 1 diabetes, polycystic ovary syndrome, metabolic syndrome), and racial differences. She is funded by the National Institutes of Health, Research Foundations and Pharmaceutical Companies and has over 200 publications. She has served in various capacities the US and international scientific communities, and has been a member of several consensus and guidelines development panels including the American Diabetes Association for youth type 2 diabetes, the Endocrine Society Childhood Obesity Guidelines 2016, the Endocrine Society PCOS Guidelines 2013, IDF for Metabolic syndrome, and ESPE for childhood insulin resistance. Dr. Arslanian has been an invited lecturer and chairperson at various international congresses and she is the recipient of several prestigious awards for her seminal work in pediatric Type 2 diabetes.

KEYNOTE SPEAKER

DR. MICHAEL KOBOR, PhD

Epigenetics in Human Health and Disease

This presentation will highlight the emerging role of epigenetic modifications at the interface between environments and the genome. Focusing on a suite of interdisciplinary human population studies, Dr. Kobor will discuss how early life adversities such as poverty and family stress leave a biological residue that can persist into adulthood and might affect cellular aging. Conceptually, this presentation provides a new perspective on the nature versus nurture debate.

BIOGRAPHY

Dr. Michael S. Kobor is a Professor in the Department of Medical Genetics at UBC, and a Senior Scientist at the Centre for Molecular Medicine and Therapeutics in the BC Children's Hospital. He was recently appointed as the Lead for the "Healthy Starts" Theme at BC Children's Hospital, an organizational structure that connects 70 clinical and basic UBC faculty members broadly interested in early-life environments at the nexus with children's health. Dr. Kobor also serves as the Director of the Program on Social Epigenetics at the Human Early Learning Partnership (HELP) at UBC's School of Population and Public Health. Dr. Kobor's own research program is focused on illuminating the developmental origins of health and disease. Building upon deep expertise in gene regulation and epigenetics developed over the course of his career, Dr. Kobor's translational research in human populations is taking a life course approach to understand human health. Through a large interdisciplinary research network with partners from child development, psychology, psychiatry, and epidemiology, these studies are deciphering the mechanisms by which environmental exposures and life experiences can "get under the skin" to persistently affect health and behaviour across the lifespan.

Dr. Kobor holds the Canada Research Chair in Social Epigenetics and is a Senior Fellow of the Canadian Institute for Advanced Research (CIFAR) Child and Brain Development Program.

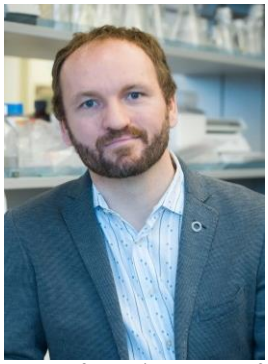
KEYNOTE SPEAKER

DR. JAMES JOHNSON, PhD

Excessive Insulin Drives Obesity, Insulin Resistance & Lifespan Shortening

Hyperinsulinemia is commonly considered to be a downstream consequence of insulin resistance and obesity, but newer models where insulin production can be directly modulated are challenging the prevailing paradigm. Genetic down-regulation of insulin/insulin-like growth factor (IGF)-1 signaling extends lifespan in invertebrates and mammals, but the role of the insulin ligand itself in altering mammalian longevity has remained controversial, in part because few models are available that can distinguish the effects of these two related hormones. A prominent role for insulin in longevity has been generally disregarded, as it is essential for glucose homeostasis, and in some cases decreased insulin signaling has been associated with greater risk of age-related disease instead of lifespan extension. Because there has been no way to separate the effects of hyperinsulinemia from insulin resistance, the physiological effects of insulin levels on mammalian healthspan and lifespan were unresolved. Throughout their natural lifespans, we characterized insulin levels, glucose tolerance, insulin sensitivity, body composition, and strength in large cohorts of male and female *Ins1*$^{-/-}$:*Ins2*$^{+/-}$ experimental mice and their *Ins1*$^{-/-}$:*Ins2*$^{+/+}$ control littermates that were fed one of two distinct diets. At 2 years of age, female *Ins1*$^{-/-}$:*Ins2*$^{+/-}$ experimental mice had ~20% reduced circulating insulin regardless of diet when compared with *Ins1*$^{-/-}$:*Ins2*$^{+/+}$ littermates. We report that rather than having negative repercussions for glucose homeostasis, decreasing insulin led to fasting glucose that was 1 mM lower, with a significantly reduced HOMA-IR, and ~15% improved insulin sensitivity in insulin tolerance tests in aged mice with reduced insulin gene dosage across both diets. Body mass and fat mass were reduced by 10% across both diets, while fat-free mass and grip strength were unchanged in mice with modestly reduced insulin. We also find that a modest reduction in circulating insulin was sufficient to impart significant lifespan extension in female mice. The pro-longevity effect of reduced insulin was not associated with altered IGF-1, and was robustly observed across two diverse diets. Autopsy analyses of each mouse suggested a generalized improvement in health span in *Ins1*$^{-/-}$:*Ins2*$^{+/-}$ mice, rather than protection from a specific cause of death. RNA-sequencing of liver samples from 30 week old mice demonstrated pan-diet and diet-specific changes in several key growth, metabolism, and longevity related pathways. In male littermates, the reduction of insulin gene dosage was not sufficient to consistently reduce circulating insulin, so we were unable to test our primary hypotheses. Our results demonstrate that a component of the insulin resistance that is observed with aging is caused by excessive insulin secretion, an observation that is incompatible with current dogma. Our study shows that moderately lowering circulating insulin, without changing IGF-1, can promote healthier aging and extend lifespan in mammals. These results have implications for the choice of personalized diets that can maintain insulin levels within a healthy range.

BIOGRAPHY



Jim Johnson is a Professor in the Department of Cellular and Physiological Sciences, and the Department of Surgery at the UBC. He joined UBC in 2004, after a post-doctoral fellowship focused on apoptosis and signal transduction in mouse and human beta-cells with Ken Polonsky and Stan Misler at Washington University in St. Louis, PhD training which focused on signal transduction controlling pituitary hormone secretion in goldfish with John Chang at the University of Alberta, and Honours Bachelor degree in Kinesiology from Lakehead University. Jim is a founding member and now Leader of the Diabetes Research Group at the Life Sciences Institute at UBC. He is Editor-in-Chief of the journal *Islets*, and on the Editorial Boards of *Diabetes* and *Endocrinology*. An expert in the fundamental biology of diabetes and related conditions, he is the author of >110 peer-reviewed articles since 2000. Breakthroughs on the mechanisms regulating beta-cell function and fate, and on the roles of insulin and insulin signaling throughout the body, have been published in prestigious and highly cited journals including *PNAS, Cell Metabolism, Nature Communications, Diabetes, Diabetologia*. His current research focuses on multiple themes, including: type 1 diabetes, type 2 diabetes, obesity, heart disease, neuroscience, pancreatic cancer, and longevity. He teaches human physiology to large and small classes and directly mentors a diverse team of students and post-doctoral fellows in his laboratory. His laboratory's work is funded by the Canadian Diabetes Association, the JDRF, the Canadian Institutes of Health Research, the Stem Cell Network, the Alzheimer's Association, the Canada Foundation for Innovation, and other agencies. Jim is actively involved in outreach on Twitter @JimJohnsonSci. Outside of science, Jim is an avid hockey player and enjoys spending time with friends and family.

KEYNOTE SPEAKER

DR. GILLIAN BOOTH, MD

Healthy Cities, Healthier Lives: Urban Environments and Risk of Diabetes

Widespread increases in physical inactivity and caloric intake have led to a global epidemic of overweight, obesity and diabetes. The reasons for these trends are multifaceted and complex. However, major drivers include increased portion sizes, the ubiquity of high-calorie, low-cost convenience foods, and a way of life that encourages sedentary behaviour, such as sitting at computers, in front of television screens, and in cars. The ongoing rise in obesity has spawned an intense search for population-level solutions to reverse these trends. One solution that is gaining momentum among public health officials is the potential to design or redesign the *built environment* in which we live—including buildings, parks, transportation systems and overall communities—to promote active, healthy living. Numerous studies have suggested a link between neighbourhood characteristics – including urban design, the presence of recreational spaces and foodscapes –and the physical activity and dietary patterns of local residents. While earlier studies were largely cross-sectional and yielded heterogeneous results; there is growing evidence from large, observational studies that neighbourhoods that provide more opportunities for walking and cycling have lower rates of obesity and diabetes. Collectively, this evidence suggests that population interventions targeting the built environment may have long-term health benefits. Further research is needed to more fully understand the impact that built environment interventions will have on levels of obesity and diabetes.

BIOGRAPHY

Gillian Booth, MD, MSc, FRCP, is a Scientist in the Centre for Urban Health Solutions, located at the Li Ka Shing Knowledge Institute of St. Michael's Hospital in Toronto. Dr. Booth is also an Adjunct Scientist at the Institute for Clinical Evaluative Sciences (ICES) and an Associate Professor in the Department of Medicine and the Institute of Health Policy, Management and Evaluation at the University of Toronto. She has received numerous awards for her research and is currently supported by a Mid-Career Investigator Award from the Heart and Stroke Foundation of Ontario. Dr. Booth's research focuses on environmental, socioeconomic, and health care factors influencing the risk of diabetes and related chronic diseases, with a major interest in the role of the built environment in perpetuating obesity-related diseases – for which she recently received a 7-year CIHR Foundation grant. Dr. Booth has made major contributions to diabetes policy and practice at both the national and provincial levels. She has served on advisory committees for the Public Health Agency of Canada's Canadian Chronic Disease Surveillance System and was the Methods Chair for the 2008 and 2013 Canadian Diabetes Association Clinical Practice Guidelines.

SELECTED TRAINEE TALKS

VIKRAM BHATIA – *Davie Lab*

Ubiquitin Carboxyl-Terminal Esterase L1 genomic Location and Function

Introduction: Ubiquitin Carboxyl-Terminal Esterase L1 (UCHL1) is a member of the peptidase C12 family and has both the enzymatic activity to remove or add ubiquitin to proteins. Removal of ubiquitin is done through the enzyme's thiol protease activity, which hydrolyzes the peptide bond at C-terminal glycine of ubiquitin. UCHL1 has a role in maintaining ubiquitin homeostasis and protein degradation. It is found in the cytoplasm and nucleus of human and mouse pancreatic β-cells. Interestingly, UCHL1 is associated with neurodegenerative diseases and pancreatic β-cell survival with Diabetes mellitus Type 2 (T2DM).
Objectives: To determine the genomic location and function of UCHL1
Methodology: Chromatin Immunoprecipitation (ChIP), ChIP sequencing (ChIP-Seq), Quantitative PCR (qPCR)
Results: We performed ChIP-Seq to determine the genomic location of UCHL1 binding sites in human prostate cancer cells (DU145) and an embryonic kidney cell line with a neuronal lineage (HEK293T). Based on ChIP-Seq data analysis, we selected and successfully validated five of these binding sites by qPCR. The binding sites were intronic sequences of the *CLIC6*, *RASGRF1, Chromosome10p15, HS3ST4* and *CFDP1*. We applied the similar approach in mouse pancreatic β-cells (MIN6) by designing primers based on the corresponding mouse sequences of human UCHL1 binding sites. Out of five sites, only three were present in the mouse. As a first step, we identified that UCHL1 binds to DNA, suggesting that UCHL1 may function to control the expression of target genes.
Conclusions: UCHL1 may be a novel regulator of genome organization and function. Ultimately, it could be a better therapeutic target in the maintenance of disease development.

ANITA DURKSEN – *Dart Research Group (iCARE)*

Objective Measures of Mental Health and Disease in Manitoba Youth Living With and Without Type 2 Diabetes

Introduction: Behavioural lifestyle interventions have generally proven ineffective for achieving clinically relevant improvements in cardiometabolic risk in adolescents with type 2 diabetes (T2D), possibly due to a lack of readiness for making lifestyle changes.
Hypothesis: We hypothesized that (1) Indigenous youth aged 10-18 years with T2D would display a lower readiness for change, compared to controls without T2D and (2) readiness for change would be associated with measures of cardiorenal risk among youth with T2D.
Methods: We performed cross-sectional comparisons of readiness for change defined by Prochaska's Transtheoretical (Stages of Change) Model for behaviour modification between Indigenous youth with T2D and controls without T2D. The main outcome measures were readiness for achieving recommended daily targets for (1) physical activity; (2) fruit and vegetable intake; (3) saturated fat intake and (4) sedentary habits determined from validated questionnaires. Secondary outcomes measures were glycated hemoglobin, 24-hr blood pressure, BMI Z score and albumin to creatinine ratio (ACR).
Results: Youth with T2D (n=137) were younger (15.2 vs 16.4 yrs; p=0.005) and had a lower BMI Z score (2.3 vs 2.7, p = 0.03) compared to controls (n=48). Youth with T2D were more likely to be in the action/maintenance stage of change for physical activity (27% vs 13%, p = 0.035) compared to controls, while no differences were observed in the readiness for daily fruit and vegetable intake (13% vs 17%, p=0.44), sedentary habits (42 vs 38%, p=0.65); or daily fat intake (44% vs 30%, p=0.09). Only 5 youth were in the action/maintenance phase for all 4 behaviours and 48 were in the action/maintenance phase for 2 or 3 behaviours. Among youth with T2D, those in the action/maintenance phase for all 4 behaviours (n=5) displayed a lower HbA1c (6.5 ± 1.1% vs 9.8 ± 2.6%; p = 0.001) and ACR (0.5 ± 0.8 vs 5.5 ± 6.8, p = 0.001), without differences in blood pressure or BMI Z score compared to those that were not (n=132).
Conclusion: Readiness for behaviour change is low among Indigenous youth with T2D but similar to Indigenous adolescents without T2D. Youth in the action/maintenance stage of change had better glycemic control and less proteinuria.

SELECTED TRAINEE TALKS

LAURA COLE – *Hatch Lab*

Impaired Cardiolipin Biosynthesis Prevents Hepatic Steatosis and Diet-Induced Obesity

Tafazzin is a transacylase that maintains mitochondrial membrane integrity and the function of the mitochondrial respiratory chain. Specifically, tafazzin maintains the content and molecular structure of the unique tetra-acyl phospholipid cardiolipin (CL) located in the inner mitochondrial membrane. Despite abundant evidence that mitochondrial dysfunction is associated with insulin resistance, little is known about the potential role of CL and tafazzin in the trajectory of this disease. To investigate the in vivo effects of tafazzin deficiency, we have utilized a mouse model with a doxycycline- inducible tafazzin shRNA knock-down. Tafazzin knock-down mice were protected against the development of obesity, hepatic steatosis and insulin resistance compared to control litter mates with both low and high-fat diets. Analysis of body composition revealed that fat mass was dramatically reduced (77%) with little effect on lean body mass (14% reduction). In both low and high-fat challenges the lack of weight gain was accompanied by whole-body hypermetabolism. We determined that mitochondrial respiration was elevated in hepatocytes but not skeletal muscle fibres isolated from tafazzin knock-down animals. Unexpectedly, the large reduction of cardiolipin in the heart and skeletal muscle of tafazzin knock-down mice was not observed in the liver. As a result, tafazzin knock-down mice exhibited normal hepatic mitochondrial supercomplex formation. Hepatic fatty acid-dependent oxygen consumption was also increased >4-fold when tafazzin was knocked-down. Our data indicates a coordinated increase in hepatic cardiolipin synthesis and fatty acid oxidation supported by elevated expression of mitochondrial trifunctional protein. These experiments indicate that mice deficient in tafazzin are protected against obesity, insulin resistance and hepatic steatosis. Since, the development of type 2 diabetes is closely related to hepatic steatosis and obesity, altering cardiolipin synthesis may be a novel therapeutic option for children at risk for type 2 diabetes.

MOHAMMAD GOLAM SABBIR – *Fernyhough Lab*

Novel Therapy for Diabetic Neuropathy: Studies on Muscarinic Acetylcholine Receptor type-1 Modulation of Mitochondrial Function Via Calcium/Calmodulin-Dependent Protein Kinase β

Introduction: AMP-activated protein kinase (AMPK) is an energy-sensor that is dysregulated in multiple tissues in diabetes and linked to mitochondrial dysfunction and development of neuropathy. Muscarinic acetylcholine receptor type-1 (M1R) is a metabotropic G-protein coupled receptor that regulates AMPK and has been targeted for therapeutic intervention in diabetic neuropathy. The specific M1R antagonist, muscarinic toxin 7 (MT7), can cause elevations in AMPK phosphorylation, mitochondrial function and neurite outgrowth in cultured adult sensory neurons. Ca^{2+}/calmodulin-dependent protein kinase kinase β (CaMKKβ) is a kinase that amplifies Ca^{2+} signals through a series of phosphorylation events and regulates cellular metabolism, in part, via phosphorylation of AMPK. In the present study, we tested the hypothesis that MT7/M1R activation of CaMKKβ could up-regulate mitochondrial function in neurons derived from both control and type-1 diabetic rats.
Methodology: Post-translational modifications of CaMKKβ were studied by isoelectric focusing. Live imaging of CaMKKβ localization in adult neurons was performed using fluorescently labelled halo-CaMKKβ transgene over-expression. CaMKKβ expression was knocked down using siRNA and effects on mitochondrial function were analyzed using the SeaHorse XF24 flux-analyzer.
Results: The negatively charged fraction of native CaMKKβ significantly decreased in diabetic cultures (suggestive of altered phosphorylation status). Treatment with 100nM MT7 for 24h significantly altered the charged status of native CaMKKβ in neuronal cultures from both control and streptozotocin (STZ)-induced diabetic rats which correlated with differential intracellular localization of CaMKKβ. The siRNA mediated silencing of CaMKKβ in sensory neurons significantly decreased the AMPK phosphorylation level. Treatment with MT7 significantly increased the spare respiratory capacity (P value =0.02) and rescued the CaMKKβ knockdown-induced decrease in ATP production.
Discussion: Augmentation of mitochondrial function and neurite outgrowth by MT7 may be mediated through activation of CaMKKβ and AMPK signaling that may have therapeutic implications.

SELECTED TRAINEE TALKS

LISA CHU – *Timmons Lab (McMaster University)*

Effect of 7 Days of Exercise on Metabolic Flexibility in Children with Obesity

Background: The capacity to match carbohydrate (CHO) oxidation with CHO availability (i.e., metabolic flexibility (MetFlex)) is important, especially for children at risk for type 2 diabetes. In adults, impaired MetFlex is associated with insulin resistance (IR), which can be improved with as little as 7 days of exercise. The responsiveness of MetFlex and IR to short-term exercise training in children is unknown. We hypothesized 7 days of exercise would improve MetFlex and IR in children with obesity.
Methods: Eight boys and 4 girls completed 2 visits before (PRE) and after (POST) exercise training. At visit 1, fasting blood work was collected, and anthropometry and aerobic fitness ($\dot{V}O_{2max}$) assessed. At visit 2, a ^{13}C-enriched CHO drink was ingested before exercise (3 x 20 min bouts) at 45% $\dot{V}O_{2max}$. Breath samples were collected to calculate oxidative efficiency of exogenous CHO (MetFlex). Stationary bicycles were transported to participants' homes for supervised sessions, alternating between continuous (3 x 15 min at 80% HR_{max}) and high intensity interval exercise (6 sets of 4 x 15 sec sprints). Visits 1 and 2 were repeated at least 48-h after exercise training.
Results: There were no improvements in MetFlex after exercise training (PRE: 20.7 ± 1.8%, POST: 18.9 ± 4.9%, p=0.22). MetFlex increased by ~2.3% in 5 children, did not change in 2 children, and decreased by ~6.4% in 5 children. HOMA-IR also did not improve (PRE: 8.7 ± 4.6, POST: 8.1 ± 6.0, p=0.51).
Conclusion: Seven days of exercise training did not improve MetFlex or HOMA-IR in children with obesity. Future research is warranted to look at exercise volume, and sex and pubertal effects on the early responsiveness of IR and MetFlex to exercise therapy.

ALLISON FEELY – *McGavock Research Group*

Prevalence and Determinants of Dysglycemia in Youth in Canada

Background: Population-based rates of prediabetes or dysglycaemia (i.e. elevated A1C) among youth in Canada are not well described. Moreover, the biological and socioeconomic determinants of an elevated A1C in youth remain poorly understood.
Methods: Youth aged 6-19 years who participated in the first (2007-2009) or second (2009-2011) cycles of the Canadian Health Measures Survey (CHMS) were included in our analyses. The primary outcome, dysglycaemia was defined using A1C guidelines established by the American Diabetes Association (ADA: 5.7%-6.4%) and Canadian Diabetes Association (CDA: 6.0%-6.4%). Various biological and socioeconomic determinants were compared between healthy and dysglycaemic youth using two sample t-tests and χ^2 tests. Age stratified regression was performed to adjust for physical activity.
Results: Of the 3449 youth studied, 785 (22.8%) and 179 (5.2%) displayed dysglycaemia according to ADA and CDA definitions, respectively. Youth with dysglycaemia (ADA definition) were more likely to be male (55.4 v 50.6%, p=0.02), non-white (24.8 v 14.6%, p<0.001) and obese (16.2 v 10.8%, p<0.001). Dysglycaemia in youth was more common in those living in households with middle income adequacy (32.6 v 26.8%, p=0.006) and lower levels of parental education (high school or less, 15 vs 11.4%, p=0.007). Similar associations were found using CDA definition. In the adjusted logistic regression model (age ≥12y), significant predictors were age, race, income adequacy, geographic region, obesity (OR=1.60, 95% CI: 1.08-2.35) and physical activity (monthly frequency of activity longer than 15 minutes, OR=0.97, 95% CI: 0.95-0.99).
Conclusion: Nearly 1 of every 5 youth in Canada are at risk for type 2 diabetes, based on early elevated A1C. Elevated A1C in youth is associated with social determinants of health and some lifestyle factors and both should be addressed in prevention efforts.

POSTER ABSTRACTS

POSTER #1

The glycemic and antioxidant responses to Saskatoon berry yogurt

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Introduction: The Canadian Diabetes Association estimates that 22.1% of Canadians have pre-diabetes. Berry phenolic compounds have been shown in cell culture and animal models to have hypoglycemic effects and lower the oxidative stress associated with diabetes. The addition of Saskatoon berry powder (SBP) to a low glycemic index (GI) food like yogurt may provide additional benefits to people with pre-diabetes.
Objective: To determine the effect of yogurt fortified with SBP on post-prandial plasma glucose and total antioxidant capacity (TAC) compared to yogurt without SBP and white bread.
Method: A randomized, controlled, cross-over trial was conducted at the I.H. Asper Research Institute. 12 healthy volunteers were given one of 3 foods containing 25g of available carbohydrate at 4 visits in random order: 1) SBP yogurt; 2) yogurt without SBP; 3) white bread (2 visits). Plasma concentrations of glucose and TAC were measured at fasting and 15, 30, 45, 60, 120 and 180 minutes after eating the foods. Plasma glucose iAUC (incremental area under the curve) from fasting to 120 minutes was calculated.
Results: The SBP yogurt (GI = 52.1) had a lower glucose iAUC compared to white bread (p=0.026). The glucose iAUC from yogurt without SBP was not significantly different from the other foods. There was a trend towards increasing TAC values at 45 and 90 minutes with the SBP yogurt (p<0.1), but not with the white bread.
Conclusion: Our results suggest that SBP fortified yogurt may qualify as a low GI food. Therefore, future studies should investigate higher doses and a larger population size that includes people with pre-diabetes.

POSTER #2

Xenin affects lipid metabolism in mouse white adipose tissue through central actions

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Introduction
Gut hormones are involved in the regulation of energy balance. Xenin is a 25-amino acid peptide produced by a subset of intestinal K-cells and is released into circulation after a meal. Central administration of xenin reduces food intake in rodents. Feeding-suppressing effect of xenin is mediated via neurotensin receptor-1 (Ntsr1) and Ntsr1 knockout mice develop mild obesity. These findings suggest the possibility that xenin acts as an endogenous satiety factor and plays a role in the regulation of whole body metabolism. However, little is known about central effect of xenin on body weight regulation and adiposity. Therefore, we tested the hypothesis that enhanced central action of xenin leads to changes in gene and protein expression of lipid metabolism in adipose tissue towards reducing adiposity.

Methodology
Male obese *ob/ob* mice underwent cannulation into the lateral ventricle and received 2 intracerebroventricular (i.c.v.) injections of xenin (5 □g/injection) or control vehicle at 1000h and 2200h under *ad libitum* fed condition. Body weight and food intake were measured over a 24-h period. Mice were euthanized 12 h after the second injection and their epididymal white adipose tissues (WAT) were isolated for RNA and protein analyses.

Results
I.c.v. xenin treatment significantly reduced 24-h food intake and body weight change during a 24-h period compared to the vehicle control. It significantly increased adipose triglyceride lipase (*Atgl,* 52.1%) and beta-3 adrenergic-receptor (*Adrb3,* 76.8%) mRNA levels in WAT. Xenin increased phosphorylation of hormone sensitive lipase (HSL) at Ser^{660} (30.3%) and reduced fatty acid synthase (FASN, 41.5%) levels in WAT.

Conclusion
Enhanced central action of xenin alters expression of lipid metabolism-related genes and proteins towards reducing lipogenesis and increasing lipolysis in WAT. These changes may contribute to xenin-induced weight reduction by reducing amount of stored fats in adipose tissue.

POSTER #3

Altered fatty acid and mitochondrial metabolism in the liver of pregnant adiponectin-deficient mice contributes to insulin resistance and gestational diabetes mellitus

Brittany L. Moyce, Laura K. Cole, Bo Xiang, Mario A. Fonseca, Christine A. Doucette, Grant M. Hatch and Vernon W. Dolinsky

Introduction: Gestational diabetes mellitus (GDM) is a common pregnancy-related health condition. While genetics, lifestyle and diet contribute to development of GDM, evidence suggests that low levels of adiponectin increases the risk for GDM. Adiponectin is a fat derived hormone that improves the sensitivity of tissues to insulin. We hypothesize that adiponectin deficiency causes fatty liver during pregnancy, ultimately contributing to the development of GDM.

Methods: We compared the glucose and insulin tolerance of pregnant (3rd trimester) adiponectin-/- (strain B6;129-*Adipoq*^{tm1Chan}/J) and wild-type mice, and assessed parameters of hepatic metabolism, including mitochondrial function and fatty acid metabolism. We assessed the impact of adiponectin supplementation by administering adenovirus mediated full length adiponectin at the end of the second trimester of pregnancy, and comparing to control containing GFP.

Results: In the third trimester, pregnant adiponectin-/- mice exhibited fasting hyperglycemia regardless of diet (9.2mmol/L vs. 7.7mmol/L in controls, $p<0.05$). These mice display impaired glucose and insulin tolerance, and elevated insulin and leptin levels relative to wild-type controls. Pregnant adiponectin-/- mice develop hepatic steatosis, including a 3-fold elevation in hepatic triglycerides ($p<0.05$). This was associated with altered hepatic lipid metabolism, including a 2.5 fold increase in fatty acid synthase expression ($p<0.05$), elevated circulating free fatty acids, triglycerides and cholesterol. Nearly 2-fold reduction ($p<0.05$) in maximal mitochondrial respiration was observed via oxidative flux analyzer in hepatocytes of adiponectin -/- mice. Gestational weight gain and food consumption were similar in knockout andwild-type mice.. Adiponectin supplementation to pregnant adiponectin-/- mice significantly improved glucose tolerance, prevented fasting hyperglycemia, and attenuated fatty liver development.

Conclusion: Results show that adiponectin deficiency is associated with altered hepatic lipid metabolism and hepatic steatosis during pregnancy. Consequently, adiponectin deficiency contributes to med-gestation insulin resistance and hyperglycemia characteristic of GDM. Moreover, adiponectin supplementation rescues the effects of adiponectin deficiency on insulin sensitivity and hepatic lipid metabolism.

POSTER #4

An Evaluation of Progression and Regression of Albuminuria in Youth with Type 2 Diabetes

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Background: Youth with type 2 diabetes (T2D) are at high risk for early kidney injury in the form of albuminuria and progression to end-stage kidney disease. The natural history and risk factors for progression of proteinuria over time is unknown.
Objectives: 1. Evaluate changes in albuminuria (progression or regression) during follow-up based on urine albumin:creatinine ratio (ACR) category. 2. Assess associations between conversion status and clinical risk factors.
Methods: Youth with T2D from The *I*mproving renal *C*omplications in *A*dolescents with T2D through *RE*search (iCARE) Manitoba cohort study with at least one annual follow-up were included. The main outcome of interest was albuminuria status over time stratified into 3 categories: 1. non-converters (NC) (remained normal (ACR <2mg/mmol) or microalbuminuria (MA) (≥2-20mg/mmol)) 2. converters (C) (worsened or remained macroalbuminuria (≥20mg/mmol)) and 3. reverters (R) (improved). Baseline descriptive characteristics compared across categories included: age, sex, BMI z-score, duration of diabetes, baseline glycated haemoglobin (A1c), glomerular filtration rate (GFR), and hypertensive load.
Results: 121 youth with T2D were studied. Median ACR was 0.72 at baseline, 1.5 at 1 year (n=71), 1.5 at 2 years (n=74) and 3.5 mg/mmol at 3 years (n=8). At baseline, 28.1% had albuminuria. 63.6% remained non-converters (49.6% normal throughout and 14.0% remained MA), 22.3% were converters and 11.6% were reverters. There were no significant differences in age, sex, duration of diabetes, BMIzscore, GFR, diastolic blood pressures or A1c between groups. Converters had lower systolic blood pressure loads (wake: 18.1% (C) vs. 29% (NC) vs. 63.9% (R); p=0.02 and sleep= 37.5% (C) vs. 45.4% (NC) vs. 75% (R); p=0.01)).
Conclusions: Youth with T2D have high rates of albuminuria. Rates of progression are also high, however a small proportion also improve/revert over time. Traditional risk factors do not predict progression in youth, and novel biomarkers need to be explored.

POSTER #5

Does resveratrol protect against gestational diabetes and the risk for heart disease in the offspring?

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Introduction: Current rates of gestational diabetes mellitus (GDM) are about 5-10% of pregnant women. GDM increases the risk of cardio-metabolic disease in mothers, and also predisposes offspring to obesity, insulin resistance and heart disease. Resveratrol (Resv), is a polyphenolic molecule produced by plants that has anti-oxidant characteristics and positive metabolic health effects. We hypothesize that 150 mg/kg administration of Resv will reduce maternal hyperglycemia and thus protect the offspring from GDM-induced heart disease.

***Methods*:** 6 weeks prior to mating, female rats received a high fat and sucrose (HFS) diet (45% kcal fat) to induce GDM, while lean control females received a low fat (LF) diet (10% kcal fat). At the beginning of the third trimester, the diets of a subgroup of pregnant HFS-fed rats was supplemented with Resv (150 mg/kg), thus creating 3 experimental groups (GDM, Lean, GDM+Resv). After weaning, offspring were randomly assigned either a HFS or LF diet for 12 weeks. Functional and morphometric analyses of offspring hearts were assessed by echocardiography using a Vevo 2100 ultrasound.

Results: Maternal Resv supplementation rescued the body weight trajectories in GDM+Resv offspring compared to GDM offspring ($p<0.05$), to the same level as lean control offspring. 15 week-old offspring of GDM+Resv mothers exhibited a 30% decrease in left ventricular posterior wall thickness when compared to GDM offspring ($p<0.05$). Functional parameters were unchanged among all 3 offspring groups at 15-weeks of age.

Conclusion: Taken together, our results show that administration of Resv prevents two risk factors for heart disease, namely obesity and cardiac hypertrophy in offspring exposed to GDM. Therefore, Resv could be administered to mothers diagnosed with GDM, in order to prevent negative health outcomes in their offspring.

POSTER #6

Gestational diabetes mellitus induces hepatic steatosis in old-age rat offspring

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Introduction: Gestational diabetes mellitus (GDM) is the most common complication of pregnancy. Children of mothers with GDM are at an increased risk of developing metabolic diseases later in life; though the mechanisms responsible are unknown. Elevated serum fatty acid levels contribute to triglyceride accumulation in peripheral organs, such as the liver. Pathologically, this can lead to hepatic steatosis. We hypothesize that exposure to GDM induces hepatic steatosis in old-age rat offspring through altered energy metabolism.

Methods: To induce GDM, female Sprague-Dawley rats were fed a high fat (45% kcal) and sucrose (HFS) diet 6 weeks prior to mating, throughout pregnancy and lactation. Lean control females received a low fat (LF; 10% kcal) diet. To assess the interaction between the prenatal GDM exposure and the postnatal diet over the entire life course of the offspring, after weaning offspring were randomly assigned to HFS or LF diets. Biological data was collected from old-age offspring at 12-months of age. Biochemical assays quantifying liver glycogen and triacylglycerol levels were performed in addition to immunoblotting for the expression of key proteins involved in lipid metabolism.

Results: Liver triacylglycerol levels were increased 2.2-fold in GDM offspring fed a HFS diet when compared to Lean controls ($p<0.01$). Liver glycogen content was unchanged among all offspring. The expression of both acetyl-CoA carboxylase and fatty acid synthase that are involved in lipid synthesis were reduced ($p<0.005$, $p<0.05$ respectively) in GDM-HFS offspring. Mitochondrial electron transport chain complex expression was unchanged in offspring exposed to GDM in utero.

Conclusions: Our data suggests that exposure to GDM induces hepatic steatosis in old-age rat offspring through increased triacylglycerol accumulation and alterations in expression of key proteins that control lipid metabolism. Taken together these results suggest that offspring exposed to GDM are at greater risk of developing metabolic diseases in old-age.

POSTER #7

GLUT14 (*SLC2A14*): Genomic Locus, Glucose Transport and Potential Inhibitors

Haonan Zhouyao, Mandana Amir Shaghaghi, Peter Eck

SLC2A14, encoding GLUT14, is an uncharacterized member of the facilitative glucose membrane transporter family. Its expression was originally described to be within human testis only[1]. However, its genetic variations had recently been associated with Alzheimer's and Inflammatory Bowel Disease, warranting further characterization of the genomic locus, expression pattern, and function.

The *SLC2A14* genomic locus contains twenty exons covering 103,477 nucleotides. The exon utilization is tissue specific for brain and testis. Major expression was found in testis, medium level expression in colon, small intestine, lung, and ovary[2]. When expressed in *Xenopus lavis* oocytes, GLUT14 mediated radio-labelled deoxy-glucose uptake. With the presence of crude plant extracts, reduced uptake of radio-labelled deoxy-glucse mediated by GLUT14 was observed.

Our data provide an explanation for existing *SLC2A14* genetic associations with common and complex diseases. It provides the functional basis for future studies on the disease mechanisms. Ultimately, genetic variations in *SLC2A14* could be used as disease predictors in prevention and early intervention.

Key References

1. Fine, P.V.A., Miller, Z.J., Mesones, I., Irazuzta, S., Appel, H.M., Stevens, M.H.H. (2006). The growth defense trade-off and habitat specialization by plants in amazonian forest. Ecology, 87, S150-S162.
2. Pandey, A., Tripathi, P., Pandey, R., Srivatava, R., and Goswami, S. (2011). "Alternative therapies useful in the management of diabetes: A systematic review." Journal of Pharmacy and Bioallied Sciences, 3(4), 504-512.
3. Kwon, O., Eck, P., Chen, S., Corpe, C. P., Lee, J. H., Kruhlak, M., and Levine, M. (2007). "Inhibition of the intestinal glucose transporter GLUT2 by flavonoids." FASEB Journal, 21(2), 366-377.
4. Song, J., Kwon, O., Chen, S., Daruwala, R., Eck, P., Park, J. B., and Levine, M. (2002). "Flavonoid inhibition of sodium-dependent vitamin C transporter 1 (SVCT1) and glucose transporter isoform 2 (GLUT2), intestinal transporters for vitamin C and glucose." Journal of Biological Chemistry, 277(18), 15252-15260.

POSTER #8

Targeting of Bnip3 Alternative Splicing to Mitigate Perinatal Hypoxia Injury

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Introduction: Perinatal hypoxia negatively impacts neonatal growth and development, which has been shown to impact cardiometabolic health. Bnip3 is a hypoxia-regulated cell death gene; previously we have shown that the cytoprotective drug Misoprostol (a prostaglandin E2 agonist) suppressed Bnip3 expression. Additionally, Bnip3 is subjected to alternative splicing to produce pro-death and pro-survival isoforms. I hypothesize that the protective effects of Misoprostol are a consequence of the effects of alternative Bnip3 variants on mitochondrial function and/or expression of survival genes.

Methods: In a neonatal rat model treated with Misoprostol, semi-quantitative RT-PCR was used to identify the splicing of full length Bnip3 (Bnip3FL) into the splice variant Bnip3ΔExon3. Secondly neonatal rat cardiomyocytes to evaluate mitochondrial respiration by extracellular flux analysis. Thirdly, I used fluorescent-tagged biosensors in a human cell line (HCT-116) expressing two Bnip3 isoforms to determine their respective effects on cell viability, mitochondrial function and calcium, and intracellular localization of the transcription factors NFAT and HDAC5.

Results: In rat pup hearts, Misoprostol increased Bnip3ΔExon3 expression compared to heart tissue of untreated pups, Misoprostol also restored the decrease in mitochondrial respiratory capacity caused by hypoxia in cells expressing the two Bnip3 isoforms, Bnip3FL caused an 8-fold increase in cell death, an effect rescued by Bnip3ΔExon3. Bnip3ΔExon3 decreased 25% of mitochondrial calcium accumulation caused by Bnip3FL (0.0019 vs 0.0026, $p < 0.05$)., Bnip3ΔExon3 promoted closure of Bnip3FL-induced mitochondrial permeability transition. Furthermore, Bnip3ΔExon3 redirected calcium to the nucleus and modified the activity of transcription factors in cells expressing Bnip3ΔExon3, as evidenced by a 5-fold increase in active NFAT and a 50% reduction in active HDAC5.

Conclusion: Bnip3ΔExon3 expression preserves mitochondrial function and regulates the activity of transcription factors associated with pro-survival genes. These data further elucidate the mechanisms underlying the protective effects of Misoprostol, and its potential use in mitigating perinatal hypoxic injury.

POSTER #9

Readiness for change among Indigenous youth with type 2 diabetes

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Introduction: Behavioural lifestyle interventions have generally proven ineffective for achieving clinically relevant improvements in cardiometabolic risk in adolescents with type 2 diabetes (T2D), possibly due to a lack of readiness for making lifestyle changes.
Hypothesis: We hypothesized that (1) Indigenous youth aged 10-18 years with T2D would display a lower readiness for change, compared to controls without T2D and (2) readiness for change would be associated with measures of cardiorenal risk among youth with T2D.
Methods: We performed cross-sectional comparisons of readiness for change defined by Prochaska's Transtheoretical (Stages of Change) Model for behaviour modification between Indigenous youth with T2D and controls without T2D. The main outcome measures were readiness for achieving recommended daily targets for (1) physical activity; (2) fruit and vegetable intake; (3) saturated fat intake and (4) sedentary habits determined from validated questionnaires. Secondary outcomes measures were glycated hemoglobin, 24-hr blood pressure, BMI Z score and albumin to creatinine ratio (ACR).
Results: Youth with T2D (n=137) were younger (15.2 vs 16.4 yrs; p=0.005) and had a lower BMI Z score (2.3 vs 2.7, p = 0.03) compared to controls (n=48). Youth with T2D were more likely to be in the action/maintenance stage of change for physical activity (27% vs 13%, p = 0.035) compared to controls, while no differences were observed in the readiness for daily fruit and vegetable intake (13% vs 17%, p=0.44), sedentary habits (42 vs 38%, p=0.65); or daily fat intake (44% vs 30%, p=0.09). Only 5 youth were in the action/maintenance phase for all 4 behaviours and 48 were in the action/maintenance phase for 2 or 3 behaviours. Among youth with T2D, those in the action/maintenance phase for all 4 behaviours (n=5) displayed a lower HbA1c (6.5 ± 1.1% vs 9.8 ± 2.6%; p = 0.001) and ACR (0.5 ± 0.8 vs 5.5 ± 6.8, p = 0.001), without differences in blood pressure or BMI Z score compared to those that were not (n=132).
Conclusion: Readiness for behaviour change is low among Indigenous youth with T2D but similar to Indigenous adolescents without T2D. Youth in the action/maintenance stage of change had better glycemic control and less proteinuria.

POSTER #10

Patient reported satisfaction with a novel combined care clinic for children with type 2 diabetes and renal complications.

Julie Halipchuk, Brandy Wicklow, Megan Bale and Allison Dart

Background: With both T2D increasing in youth <18 years of age, and a high burden of kidney disease reported in youth with T2D, a need for this novel clinic was demonstrated. The objective of this study is to describe patient satisfaction with a combined nephrology and diabetes model of care, established in 2013, for youth with T2D at high risk of end stage renal disease.
Methodology: Criteria for clinic attendance include: T2D, <17years of age, macroalbuminuria on 1 random urine sample, persistent microalbuminuria (ACR >10mg/mmol x2 samples within 6 months) and/or, eGRF <90 ml min/1.73m2. For 2 years, 24 patients were followed, with 8 patients seen per clinic every 3 months. Patients are seen by the endocrinologist, nephrologist and renal nurse, and attend a group education session with diabetes educators. In 2015, patient satisfaction was assessed utilizing a survey tool that included both open ended questions and Likert scales, and was administered to patients and their family during a clinic visit by a single team member.
Results: Participants had a mean age of 14.8 years. 17 of 24 patients agreed to participate in this survey. 76% of patients preferred the current model of a joint clinic to separate diabetes and nephrology encounters. 76% preferred group education as a method of learning over an individual appointment with the educator, 65% agreed that they felt welcome and safe in group, though 35% reported being too shy or scared to talk in a group setting. The majority of participants reported getting good care from their diabetes and kidney team (82%).
Conclusions: The clinic has been successful in delivering a unique model of care with an interactive educational component to families. Family satisfaction with this current model is high, though continued efforts to include the patient voice are necessary.

POSTER #11

Patterns and Policy: Insulin Treatment Regimens and Blood Glucose Test Strip Utilization

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Background: Considerable attention has been paid to the rising costs of blood glucose test strip (BGTS) use, with several provinces imposed limits on the number of BGTS that will be covered within a year. These policies have tended to treat insulin-treated persons as a singular group, capping BGTS coverage at a single number for all insulin users, regardless of their treatment regimen. The objective of this study was to conduct a utilization review of BGTS in insulin users, evaluate patterns in insulin use, and contrast these findings against current BGTS policy.
Method: BGTS usage was examined in a cohort of insulin users with type 1 and type 2 diabetes, stratified by insulin regimen, over a 12-year period (2001-13) using the population-based administrative data in Manitoba, Canada.
Results: Total BGTS usage more than doubled with annual costs increasing from $4.3 to $9.5 million. Over the same period, the number of insulin users also more than doubled. However, daily BGTS use has remained stable at 1.9 strips/day/person since 2004. Frequency of glucose testing below that recommended in current guidelines was evident, with 14% and 16% of insulin users with type 1 and type 2 diabetes filling no BGTS prescriptions, and a further 21% (type 1) and 31% (type 2) of persons using < 1 strip/day. The 90th percentile of usage was 5.6 and 3.4 strips/day for type 1 and type 2 diabetes, respectively.
Conclusions: The number of BGTS used per insulin user per day has been stable for most of the past decade, with the vast majority of use falling well below provincial insurance caps. The amount of low-level testing (0 to <1 strip/day) suggests that greater attention should be directed to ensure a safe level of testing in all insulin users.

POSTER #12

Nucleosomal Response Pathway and Transcriptional Programming

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Introduction: The RAS-mitogen-activated protein kinase (MAPK) pathway has been deregulated in many diseases. Induction of the RAS-MAPK pathway triggers the initiation of transcriptional responses, which drive the cells towards cell proliferation. Mitogen and stress-activated kinases 1/2 (MSK1/2), act downstream of the MAPK signalling pathway and phosphorylate histone H3 at S10 (H3S10ph) or S28 (H3S28ph) (nucleosomal response) at regulatory region of immediate early genes (IEGs), but the extent of effects and mechanisms has not been completely understood.
Objectives: To investigate the nucleosomal response pathway and transcriptional programming.
Material and Methods: RNA-sequencing, RT-qPCR, Co-Immunoprecipitation, Sequential-ChIP, Immuno-FISH).
Results: RNAseq results validated by RTq-PCR on primary human fibroblast cells (CCD1070SK70) and Mouse Fibroblast (10 T½) show that MAPK mediated nucleosomal response pathway triggers IEGs transcription. MSK inhibitor H89 reduced the expression of IEGs. Immuno-FISH results of *JUN* and *COX2* genes in primary human and mouse fibroblast cells show that MSK-catalyzed H3S10 and H3S28 phosphorylation are located at distinct nuclear sites which suggested that these do not coexist on the same histone tail. Sequential ChIP and Immuno-FISH analyses show that epi-alleles of IEGs are transcriptionally active regardless of phosphorylation site (H3S10ph/H3S28ph). Our co-IP experiments show that H3 modified at S28ph is associated with K27ac and K14ac but not at K9ac, while H3 modified at S10ph is associated with K9ac but not in K14ac and K27ac. Both H3S28ph and H3S10ph are modified at K4me1. The level of H3S28ph is responsive to inhibition of histone deacetylase and CBP. H3S28ph, but not H3S10ph, is associated with H3K27ac, providing evidence that H3K27ac guides MSK to phosphorylate H3 at S28.
Conclusions: MSK-catalyzed phosphorylation of H3S10 and H3S28 are located at different distinct nuclear sites and phosphorylation events are independent of each other.

POSTER #13

Increased SIRT3 expression in the mouse heart improves oxidative stress resistance and cardiac function in doxorubicin-treated C57BL/6 mice

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Background: More people die annually from cardiovascular disease (CVD) than from any other disease. A diagnosis of type 2 diabetes (T2D) increases the risk of developing CVD 2-3 fold. Doxorubicin (DOX) is a cardiotoxic agent, however the mechanisms that lead to CVD following DOX administration share similar characteristics as heart failure resulting from other underlying cardiovascular disorders. DOX interferes with the electron transport chain (ETC) causing inefficient electron transfer and the production of reactive oxygen species (ROS). SIRT3 is highly expressed in cardiac myocytes and regulates mitochondrial respiration and oxidative stress resistance enzymes such as superoxide dismutase-2 (SOD2). We hypothesize that increasing SIRT3 expression in the hearts of C57BL/6 mice will reduce DOX-induced cardiotoxicity and improve cardiac function.

Methods: We utilized two unique transgenic mouse lines that express either a truncated SIRT3 (M3-SIRT3) without mitochondrial localization or a full length SIRT3 (M1-SIRT3) that localizes to the mitochondria only in the heart. 3-month old C57BL/6 mice were treated with saline or 8 mg/kg doxorubicin for 4 weeks. Transthoracic echocardiography was performed using the Vevo 2100 ultrasound system (VisualSonics Inc.). FRVCs were isolated from the hearts of e20 offspring and stained with MitoSOX to quantify mitochondrial ROS production.

Results: Administration of DOX to non-transgenic mice increased isovolumetric relaxation time and decreased cardiac output ($p < 0.05$). These effects were attenuated in the DOX treated M1-SIRT3 transgenic mice ($p < 0.05$). Consistent with the improvement in these cardiac parameters, the DOX-treated M1-SIRT3 transgenic mice had reduced levels of acetylated proteins (1.8-fold, $p < 0.05$) and increased SOD2 (2.6-fold, $p < 0.05$) and SERCA2a expression (2.1-fold, $p < 0.05$) compared to DOX treated controls.

Conclusions: These results suggest that increased expression of SIRT3 in the mitochondria is sufficient to attenuate DOX-induced cardiac dysfunction. These improvements may involve increased SOD2 and SERCA2a expression in association with reduced ROS levels.

POSTER #14

Intensive Gestational Glycemic Management and Childhood Obesity: A Systematic Review and Meta-Analysis

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Background: Hyperglycemia in pregnancy is associated with increased risk of offspring childhood obesity. Treatment reduces macrosomia, however it is unclear if this effect translates into a reduced risk of childhood obesity. We performed a systematic review and meta-analysis of randomized controlled trials to evaluate the efficacy and safety of intensive glycemic management in pregnancy in preventing childhood obesity.

Methodology: We searched MEDLINE, EMBASE, CENTRAL, and ClinicalTrials.gov up to February 2016 and conference abstracts from 2010 to 2015. Two reviewers independently identified randomized controlled trials evaluating intensive glycemic management interventions for hyperglycemia in pregnancy and included four of the 383 citations initially identified. Two reviewers independently extracted trial-level data with piloted forms and evaluated internal validity of included studies using the Cochrane Collaboration's Risk of Bias tool. Data was pooled using random effects models. Statistical heterogeneity was quantified using the I^2 test. The primary outcome was age- and sex-adjusted offspring obesity measured in childhood. Secondary outcomes were offspring waist circumference and weight in childhood, and maternal hypoglycemia during the trial (safety outcome). All outcomes were specified before the start of the review.

Results: The four eligible trials (n=767 children) similarly used lifestyle and insulin to manage gestational hyperglycemia. We found no association between intensive gestational glucose management and childhood obesity at 7-10 years of age (relative risk 0.89, 95% CI 0.65 to 1.22; 2 trials; n=568 children). Waist circumference also did not differ between treatment and control arms (mean difference −2.68 cm; 95% CI −8.17 to 2.81 cm; 2 trials; n=568 children).

Conclusion: Intensive gestational glycemic management is not associated with reduced childhood obesity in offspring but randomized data is scarce. Long-term follow up of trials should be prioritized and comprehensive measures of childhood metabolic risk could be considered as outcomes in future trials.

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POSTER #15

Protecting the Hypoxic Neonate: Misoprostol-Induced Repression of Bnip3 Through NFk-B

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Introduction: Systemic hypoxia affects more than 50% of preterm infants, negatively impacting development of the intestine and brain, as well as the infants lifelong cardiometabolic health. While the mechanism for hypoxic injury remains unclear, it appears that the genetically conserved, pro-death Bnip3 pathway may play a central role. We hypothesize that Misoprostol, an FDA approved prostaglandin receptor agonist, may activate NFk-B, which represses Bnip3, in turn protecting infants from hypoxic injury.
Methods: Both environmental hypoxia (10% oxygen) and drug treatments were applied to a neonatal rat model (n=5) to assess the effect of Misoprostol and hypoxia on hippocampal, and intestinal Bnip3 expression. Gene and protein expression were determined by RT-PCR and protein immunoblot, and compared to control treatments (normoxia and/or drug vehicle). The secondary outcome of this study used a human cell line (HCT-116) (n>45 cells) to focus on the underlying mechanism, assessed through fluorescent imaging with a plasmid-based PKA biosensor, as well as expression of wild-type and non-phosphorylatable mutants of NFk-B.
Results: In the animal study, hypoxia induced a several-fold increase ($p<0.05$) in Bnip3 protein expression in both intestine and hippocampus, which was mirrored in mRNA expression. When Misoprostol was added in hypoxic conditions, Bnip3 protein was repressed by 87.5% ($p<0.05$). In parallel *in vitro* studies, overexpression of wild-type NFk-B causes considerable reduction in Bnip3 protein expression, however when NFk-B phosphorylation was inhibited with a neutral alanine mutation, Bnip3 expression was unchanged. Finally, we show that Misoprostol induces a 3-fold increase ($p<0.01$) in intracellular PKA activation and a 1.8-fold increase ($p<0.01$) in nuclear localization of NFk-B.
Conclusion: Taken together, both animal and cell data suggests that Misoprostol activates PKA/cAMP, resulting in nuclear accumulation of NFk-B, repressing Bnip3 protein expression, which may serve to protect the developing neonate.

POSTER #16

Does sleep impact the risk for type two diabetes and poor glycemic control in adolescents?

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INTRODUCTION: Disrupted sleep and sleep duration have been associated with increased risk of type 2 diabetes (T2DM) in adults. We hypothesize that adolescents with poor sleep habits (quantity and quality) are more likely to have T2DM and worse glycemic control compared to adolescents with better sleep habits.

RESEARCH DESIGN AND METHODS: Cross-sectional study of 207 adolescents, 157 with T2DM and 50 obese or overweight controls from the *I*mproving renal *C*omplications in *A*dolescents with type 2 diabetes through *RE*search (iCARE) cohort. Study participants completed the Pittsburgh Sleep Quality Index (PSQI) as a measure of sleep duration and quality and provided serum Hemoglobin A1c (HbA1c) measures. Logistic and linear regression analyses were performed to assess the associations between sleep and presence of diabetes, measures of obesity and glycemic control respectively.

RESULTS: On average, 30-60 minutes less sleep than recommended was reported with no differences between adolescents with T2D and controls (8.53 hours vs. 7.97 hours, $p = 0.083$). Overall sleep quality was good (PSQI score ≥ 5) and nearly identical between adolescents with T2D and controls (PSQI score 5.4 vs 5.6; $p = 0.664$). Youth with T2D and "poor" sleep quality had similar glycemic control compared to those reporting "good" sleep quality (9.89% vs 9.45%%, $p = 0.308$).

Logistic analysis assessed overall sleep quality of those with T2DM and those without. There was no association between PSQI score and T2D (Odds Ratio (95% CI): 0.973 (0.864 to 1.096)). Linear regression analysis showed no association between PSQI score and HbA1c (Unstandardized Coefficient (95% CI): 0.080 (-0.077 to 0.237)). Both analyses were adjusted for BMI, weight and waist/hip ratio z-score.

CONCLUSIONS: Sleep duration and quality are not associated with the development of T2DM or glycemic control after adjusting for BMI-z score, weight z-score and waist-hip ratio z score in adolescents.

POSTER #17

Neuroprotective effect of pirenzepine and muscarinic toxin 7 is mediated through muscarinic acetylcholine type-1 receptor internalization and augmentation of ERK-CREB signaling.

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Introduction: One of the major cellular effectors of G-protein coupled receptor (GPCR) is extracellular signal-related kinase (ERK). G-protein and β-arrestin mediated signaling lead to ERK activation. The subcellular location of activated ERK determines the downstream signaling cascade including activation of transcription factors. ERK is known to phosphorylate and activate transcription factor cyclic-AMP response element-binding protein (CREB). Selective antagonism of the muscarinic acetylcholine type-1 receptor (M1R) is neuroprotective in diabetic neuropathy where distal sensory nerve terminals undergo neurodegeneration. Previously, we have shown that selective and specific M1R antagonists, pirenzepine (PZ) and muscarinic toxin 7 (MT7) respectively, induce a dose-dependent elevation in neurite outgrowth in adult sensory neurons. However, the exact mechanism is not understood. In the present study, we tested the hypothesis that MT7 and PZ binding may affect β-arrestin-mediated activation of the ERK-CREB pathway to promote axonal outgrowth in neurons derived from control and type 1 diabetic rats.
Methodology: β-arrestin recruitment and internalization of M1R was performed by blue-native PAGE and live-cell imaging. Phosphorylation of ERK and CREB were studied by isoelectric focusing and detection using phospho-specific antibodies. Intracellular localization of ERK and CREB was performed by immunofluorescent microscopy.
Results: MT7 (100nm) and PZ (1μM) caused differential β-arrestin-mediated internalization of M1R within 1h and 24h of treatment. Further, MT7 and PZ caused significant increases in the dual phosphorylation of $ERK^{(T202/Y204)}$ which reached its peak within 1h in neurons derived from control or streptozotocin (STZ)-induced diabetic rats. Increased ERK phosphorylation correlated with augmented levels of phospho-$CREB^{(Ser-133)}$ and nuclear localization of phospho-$CREB^{(Ser-133)}$.
Discussion: M1R, upon binding of PZ or MT7, is internalized through recruitment of β-arrestin which leads to the activation of ERK and increased Ser-133 phosphorylation on CREB that may augment axonal outgrowth promoting gene-expression.

POSTER #18

Does Gestational Diabetes Mellitus Program Pancreatic Islet Development and Function in the Offspring?

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Introduction: Gestational Diabetes Mellitus (GDM) affects 3-20% of pregnancies.
Offspring born from a GDM pregnancy have a higher risk of developing youth onset type 2 diabetes (T2D). Factors that link GDM pregnancy and early onset T2D are not understood.
Hypothesis: GDM predisposes offspring to impaired pancreatic islet development and function.
Methods: Female rats were fed a high fat and sucrose (HFS; 45% kcal fat) diet to induce GDM, lean controls received a low fat (LF; 10% kcal fat) diet. To determine the interaction between prenatal conditions and postnatal diets, the offspring from lean and GDM mothers were placed on LF and HFS diets, postweaning. The pancreas was isolated from newborn and 15 week-old offspring for islet morphometry and glucose stimulated insulin secretion (GSIS).
Results: Newborn offspring from GDM groups showed a 2-fold increase ($p<0.05$) in total fluorescence of insulin compared to newborns from lean groups. At 15 weeks, islet counting showed a 2-fold increase ($p<0.05$) in islet numbers in both the LF-fed and HFS-fed offspring of GDM dams compared to the offspring of lean dams. Insulin immunofluorescence staining showed a 2-fold decrease ($p<0.05$) in total fluorescence in beta cells of HFS-fed offspring from both lean and GDM groups. GSIS assays indicated a 50% reduction in GSIS by islets isolated at 15 weeks from HFS-fed offspring of GDM dams compared to HFS-fed offspring of lean dams ($p<0.05$).
Conclusions: The increased insulin content and islet number in the offspring of GDM dams may be an adaptive response to hyperglycemia during pregnancy. However, exposure to GDM impaired the glucose-responsiveness of insulin secretion by the islets. Further, HFS-fed offspring of lean and GDM dams have reduced insulin content in the beta cells. Our research suggests that GDM is an important factor driving islet dysfunction and contributing to pediatric T2D.

POSTER #19

INSULIN ENHANCES AMPK ACTIVITY AND MITOCHONDRIAL FUNCTION IN ADULT SENSORY NEURONS

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Background: Diabetic sensorimotor polyneuropathy affects approximately 50% of diabetic patients. There is down-regulation of AMP-activated protein kinase (AMPK) and mitochondrial dysfunction in dorsal root ganglia (DRG) in animal models of type 1 and type 2 diabetes. We hypothesized that loss of direct insulin signaling in diabetes contributes to loss of AMPK activity and mitochondrial function in DRG neurons and contributes to development of neuropathy. **Methodology:** Adult DRG neurons were cultured from age-matched control or streptozotocin (STZ)-induced type 1 diabetic rats. Neurons treated with/without insulin underwent expression analysis of genes linked to insulin signaling. In parallel, mitochondrial respiration was determined using Seahorse assay. We also quantified the effect of insulin on neurite outgrowth. For *in vivo* work age-matched control, STZ-induced and insulin-implanted (with no effect on hyperglycemia) diabetic rats were maintained for 5 months and DRG analyzed for protein expression. **Results:** Long-term insulin treatment (10 or 100nM for 2-24h) significantly ($P<0.05$) increased phosphorylation of AMPK (on T172), acetyl-CoA carboxylase (an endogenous target of P-AMPK) and P70S6K (a downstream target of Akt directing protein synthesis). Insulin also elevated mitochondrial gene expression, augmented mitochondrial oxygen consumption rate (OCR) and neurite outgrowth. No remarkable results were observed in short-term insulin treatment. *In vivo* experiments showed an improvement in insulin-implanted animals' weight and thermal sensitivity, a non-invasive indicator of neuropathy, with no impact on blood glucose levels. In DRG there was suppressed expression of pAMPK, P70S6K and mitochondrial genes in diabetic rats, and correction of P70S6K and mitochondrial gene expression in insulin-implanted rats. **Conclusion:** *In vitro* insulin elevated AMPK activity, P70S6K, mitochondrial function and neurite outgrowth. Insulin implantation prevented depression in P70S6K and mitochondrial gene expression *in vivo*. For the first time in the nervous system insulin and its signaling pathway are demonstrated to up-regulate mitochondrial gene expression and function.

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POSTER #20

Therapeutic targeting of skeletal muscle Nix in early-onset insulin resistance.

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Introduction: Fetal exposure to diabetes during pregnancy increases the risk for early onset insulin resistance in the offspring; however, the key molecular regulators responsible for fetal metabolic programming have not been characterized. Previously, we demonstrated that the expression of a mitochondrial death gene, named Nix, was elevated in the skeletal muscle of rats exposed to gestational diabetes. Here, we identify a novel phosphorylation residue, activated by clenbuterol treatment that serves to prevent Nix induced mitochondrial dysfunction in muscle cells.
Methods: Using cell and biochemical approaches, the C2C12 skeletal muscle myotubes were exposed to 200 μM palmitate, or vehicle control. To assess mitochondrial membrane potential, cells were stained with TMRM, while macro-autophagy was determined by LC3-GFP aggregation into autophagosomes (n=10). Plasmid-based PKA biosensor was used to identify clenbuterol activation. Cellular localization of Nix was determined by cell fractionation and protein expression by western blot. Phospho-peptide mapping was performed by mass spectrometry. One-way or two-way ANOVA determined multiple comparisons between groups and student t-test compared mean differences.
Results: Exposure to palmitate during differentiation resulted in mitochondrial depolarization, compared to the control myotubes ($p<0.05$). Furthermore, mitochondrial depolarization was prevented by PKA-activating drug clenbuterol ($p<0.05$). Consistent with these findings, Nix-induced mitochondrial depolarization was inhibited by
clenbuterol, or co-expression of PKA, and clenbuterol restored muscle glucose uptake levels. It has also been observed that phosphorylated version of Nix is located at the cytosol and not in mitochondria. Detailed phospho-peptide mapping of Nix, revealed a novel phosphorylation residue within the transmembrane domain of Nix. Mutational analysis of this novel phosphorylation site attenuated Nix-induced mitochondrial depolarization ($p<0.05$), without impacting Nix-induced autophagy, determined by LC3-GFP fluorescence.
Conclusions: Our data supports the hypothesis that Nix regulates mitochondrial metabolism in differentiating skeletal muscle and suggest a possible therapeutic strategy to circumvent the mitochondrial dysfunction characteristic of insulin resistance without impacting Nix's regulation of autophagy.

POSTER #21

Gestational diabetes mellitus impairs mitochondrial and cardiac function in the rat offspring

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Introduction: Gestational diabetes mellitus (GDM) is the most common complication of pregnancy. Children of mothers with GDM are at increased risk for cardiometabolic diseases later in life. Though the mechanisms responsible are unknown, mitochondrial dysfunction is associated with cardiovascular disease. We hypothesize that GDM causes mitochondrial dysfunction in the cardiac tissue of the offspring and contributes to the development of heart disease.

Methods: To induce GDM, female rats were fed a high fat (45% kcal) and sucrose (HFS) diet prior to mating, throughout pregnancy and lactation. Lean control females received a low fat (LF; 10% kcal) diet. Fetal rat ventricular cardiomyocytes (FRVCs) were isolated from the hearts of e20 offspring and mitochondrial respiration was analyzed using a Seahorse Extracellular Flux Analyzer. To assess the interaction between prenatal GDM exposure and the influence of postnatal diet over the entire life course of the offspring, offspring were randomly assigned to HFS or LF diets after weaning. Echocardiography of offspring hearts was performed at e18 and serially at 3, 6, 9 and 12-months of age using a Vevo 2100 ultrasound.

Results: Basal and maximal mitochondrial oxidation levels were reduced for glucose (35%, 68% respectively) and fatty acid (49%, 52% respectively) substrates in FRVCs isolated from GDM offspring (all $p<0.05$). Mitochondrial reactive oxygen species production was increased 1.2-fold in FRVCs isolated from GDM offspring ($p<0.05$). Fetal and 3-month old offspring exposed to GDM in utero exhibit increased left ventricle posterior wall thickness ($p<0.05$). From 6 to 12-months of age the hearts of offspring exposed to GDM exhibit increased isovolumetric relaxation time ($p<0.05$).

Conclusion: GDM reduced both mitochondrial substrate oxidation and ATP production. This was associated with early-life cardiac hypertrophy, followed by later in life diastolic dysfunction. Combined, these mechanisms put offspring of GDM mothers at greater risk of developing heart disease in adulthood.

POSTER #22

Gender differences in perception of pregnancy risk among women with gestational diabetes and their male partners

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INTRODUCTION: Gestational diabetes (GD) is a common complication of pregnancy, impacting 6-7% of pregnancies, yet little is known about how women with GD perceive risk during pregnancy and no studies have been conducted regarding the partner's risk perception. Study objectives were to determine if gender differences exist in pregnancy risk perception and to identify gender specific predictors of risk perception.

METHODOLOGY: Participants included pregnant women with an index diagnosis of GD and their male partners, recruited from two Winnipeg hospitals (N=214). Participants self-completed questionnaires, including the Perception of Pregnancy Risk Questionnaire (PPRQ). Paired t-test was used to test for significant differences between couple's PPRQ scores. Univariate analyses of 17 predictor variables were conducted separately for women and men; significant variables were entered into hierarchical multivariable linear regressions to yield final models.

RESULTS: Women had significantly higher PPRQ scores (M 39.0 out of 100, SD 17.3) than their partners (M 33.6, SD16.6; paired $t = 3.2$; $p = .002$) and for 8 of the 13 items, including risk to baby of hypoglycemia, birthweight >9 pounds, and the risk of both the woman and the baby developing diabetes later in life. Nine variables were entered into the regression model for women (adjusted $r^2 = .288$); perceived stress ($\beta = 0.32$, $p = .001$) and pre-pregnancy BMI ($\beta = 0.19$, $p = .028$) were significantly associated with risk perception. Eight variables were entered into the model for men (adjusted $r^2 = .302$); GD knowledge ($\beta = 0.24$, $p = .010$), anxiety ($\beta = 0.21$, $p = .020$), self-efficacy ($\beta = 0.17$, $p = .045$) and Winnipeg residence ($\beta = -0.18$, $p = .045$) were significantly associated with risk perception.

CONCLUSION: Gender differences exist in both level of perceived pregnancy risk and in predictors of perceived risk for women with GD and their partners. Women perceive higher levels of pregnancy risk than men.

POSTER #23

An Annual Evaluation of the Manitoba Pediatric Insulin Pump (MPIP) Program

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Background: The Manitoba Pediatric Insulin Pump program (MPIP) funds insulin pumps for children (<18 years) with type 1 diabetes. MPIP commenced in the Fall 2012.

Objective: We provide a descriptive review of MPIP in 2015 including glycemic control, rates of pump related diabetes complications, pump discontinuation, and youth transitioning to adult care.

Method: Data was retrieved from the DER-CA database. Glycemic control was evaluated by hemoglobin A1c (A1C) using a Siemens DCA Vantage Analyser prior to initiation of pump therapy, and at 6, 12 and 24 months.

Results: Between January 1 and December 31, 2015, 19 youth completed MPIP. Mean age was 13.7 years. Mean pre-pump A1C was 7.6% (n=19), while at 6 months and 1 year respectively the mean A1C was 7.8% (n= 16) and 8% (n=10).
From October 2012 to December 2015, 121 youth have initiated insulin pump therapy through MPIP. Mean pre-pump A1C was 7.7% (n=121), 7.7% (n=95) at 6 months, 7.8% (n=76) at 12 months, and 7.8% (n=27) at 24 months.
There were 2 episodes of diabetic ketoacidosis (DKA) in 2015 (2.6/100 patient years), and 1 episode of severe hypoglycaemia (1.3/100 patient years). Two youth discontinued pump therapy in 2015 and 14 transitioned to adult care.

Conclusions: MPIP provides a standardized approach to insulin pump education. Although a slight increase in A1C was observed in the 2015 cohort, deterioration was not considered clinically significant. Patients and families have identified reasons aside from improving glycemic control to initiate pump therapy. The incidence of DKA and severe hypoglycaemia were relatively low, however both remain a risk with insulin pump use. With few individuals reverting back to injections, the number of patients transitioning to adult care on insulin pump therapy is likely to continue to increase.

POSTER #24

Myocardin regulated genetic pathway modulates mitochondrial function to prevent cell death during cardiac development

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Introduction: Fluctuating maternal glucose levels during gestational diabetes mellitus increases the risk of offspring developing diabetic cardiomyopathy, a disease linked to structural remodeling and programmed cell death. As the underlying mechanisms regulating cardiac cell death remain undefined, we hypothesize that Myocardin, a protein required for cardiac development, regulates mitochondrial function to prevent programmed cell death.
Methods: A rat cardiac tissue culture model (H9C2) was genetically manipulated or exposed to drugs (n=3) and compared to control (empty vector/scrambled or drug vehicle). The primary outcome assessed cell viability while the secondary outcome assessed mitochondrial function by measuring permeability transition pore closure, membrane potential, oxidative stress and calcium localization by fluorescent imaging. Gene and protein expression was determined by qPCR, protein immunoblot and immunofluorescence, respectively. An empty vector (ds-Red) was used to control for transfection efficiency, cells were counter-stained with nuclear Hoechst/DAPI and fluorescent signal was normalized to area.
Results: Tissue culture experiments illustrate that loss of Myocardin function reduces cell viability by 25% (95%CI, 17.74 to 31.76; $p<0.0001$), reduces mitochondrial function and reduces expression of miR-133a in comparison to control. Loss of Myocardin also increases expression of a mitochondrial death protein Nix, which is reversed by miR-133a inhibition. An *in vivo* Myocardin knockout mouse embryo model indicates an increase in cardiac Nix signal in comparison to wild type. A series of *in vitro* gain of function studies demonstrate expression of Myocardin or miR-133a independently restore cell viability ($p<0.01$), mitochondrial function ($p<0.01$) and reduces Nix protein levels. To assess the calcium crosstalk between the endoplasmic reticulum (ER) and mitochondria, Nix localized to the ER (Nix-ER) increases mitochondrial calcium uptake in comparison to control.
Conclusion: Our data supports the hypothesis that Myocardin prevents Nix-induced cell death by restoring mitochondrial function and the therapeutic potential of miR-133a molecules for improving diabetic cardiomyopathy.

POSTER #25

UCP2 expression is rhythmic in pancreatic β cells and contributes to the control of daily cycles of insulin secretion and glucose tolerance.

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INTRODUCTION: Pancreatic β cell failure is central to type 2 diabetes (T2D) development. Upregulation of uncoupling 2 protein (UCP2) is associated with obesity and T2D and impairs glucose-stimulated insulin secretion (GSIS); however, our understanding of the physiological and pathophysiological contributions of UCP2 to β cell function is unclear. Using mouse models and clonal pancreatic β cells (MIN6), we examined the physiological function of UCP2 in β cells by determining *when* UCP2 is expressed on a daily basis and *how* it controls GSIS and glucose tolerance over 24hrs.

RESULTS: Sampling synchronized MIN6 cells every 4hrs revealed that UCP2 expression is dynamic over 24hrs such that a ~2.5-fold increase ($p<0.05$) was observed between 12-24hrs, which inversely related to GSIS capacity during this timeframe. Isolated islets from wild type mice kept on a 12 hr light/12hr dark schedule showed a similar trend where GSIS capacity was highest when isolated and assessed during the dark/active phase and reduced in the light/inactive phase. Inhibition of UCP2 with genipin or genetic knockout prevented the suppression of GSIS observed in the light/inactive phase, suggesting a role for UCP2 in the inhibition of GSIS during this phase of the day. Interestingly, genetic knockout of UCP2 promoted glucose intolerance only in the lights on/inactive phase of the day. To decipher the mechanistic contribution of UCP2 to the control of temporal GSIS capacity, we further demonstrated that UCP2 temporally regulates mitochondrial membrane potential and glucose-induced ATP production, an important triggering signal for GSIS.

CONCLUSIONS: Together, our data suggests that upregulation of UCP2 during the light/inactive phase (equivalent to an overnight fast in humans) plays an integral role in the suppression of GSIS and maintenance of glucose tolerance in this phase. We suggest that UCP2 is part of an important "metabolic switch" that regulates temporal GSIS capacity. Targeting UCP2 for T2D therapies must account for its rhythmic expression and impact on glucose tolerance over 24hrs.

NOTES: