DREAM 2025 symposium
Diabetes Research Envisioned and Accomplished in Manitoba

# Diabetes Research Symposium: Making Connections for Innovation

14th Annual Diabetes Research Symposium

## Thursday, November 13, 2025

pediatric grand rounds

| | |
|---|---|
| 8:00 - 9:00 am | **12th Annual Dr. Heather Dean Lecture for Excellence in Pediatric Diabetes Research**<br>***Dr. Lindsay Crowshoe***, *University of Calgary*<br>"Social and Cultural Mechanisms of a Relational Approach to Diabetes Care with Indigenous Patients" |
| 10:20 - 10:50 am | ***Dr. Barry Lavallee***, *Keewatinohk Inniniw Minoayawin Inc.*<br>"Sovereignty: The Real Determinant of Health for First Nations" |
| 10:50 - 11:20 am | ***Dr. Lorraine Lipscombe***, *University of Toronto*<br>"The Network for Healthy Populations: Tackling Diabetes through better care, lower risk factors, and healthier living environments" |
| 11:20- 12:05 pm | ***DREAM Trainees Presentations***, *Clinical Research*<br>*Cheryle Dreaver and Tara Letandre* – "Delivering Indigenous-Led Anti-Racism Training in Healthcare Settings"<br>*Oluwatoyosi Fagbuyi* – "Beyond AIC: An Interpretive Descriptive Qualitative Study of Youth Experiences and Perceptions of Living With Type 2 Diabetes"<br>*Amrit Thandi* – "Culturally Appropriate Self-Management Education and Support for Cardiometabolic Disease Prevention in Peel Region: A Community-Engaged Approach" |
| 1:05 - 1:50 pm | ***DREAM Trainees Presentations***, *Fundamental Sciences*<br>*Marie-Sophie Lachance* – "New Apelinergic Analogues Rescue Blood Flow Perfusion and Sensory Function in Diabetic Hind Limb Ischemia"<br>Polyneuropathy: The Essential Impact of TRPM3 and M1R Antagonism"<br>*Jasmine Pipella* – "Natural Killer Cell Surveillance Eliminates Stressed Beta Cells in Type 1 Diabetes"<br>*Khushali Trivedi* – "Sirtuin-3 Deficiency in the Liver is Associated with Mitochondrial Dysfunction and Hepatic Steatosis in Gestational Diabetes" |
| 1:50 - 2:20 pm | ***Dr. Erin Mulvihill,*** *University of Ottawa*<br>"Empathy in Action: Making Connections that Drive Innovation" |

# greetings

## from the CHRIM interim co-CEOs

**Drs. Andrew Halayko, Brandy Wicklow and Cheryl Rockman-Greenberg**
Co-Chief Executive Officers (CEO), CHRIM

Welcome to the 14th annual DREAM research symposium!

The DREAM symposium has become a platform to highlight recent discoveries by DREAM researchers and their trainees that lead to improvement of the health of children living with, or at risk for diabetes. In addition, the symposium provides an opportunity to hear from some of the world's best and brightest stars in diabetes and health research. The symposium will begin with the 12th Annual Heather Dean Lecture in Excellence in Diabetes by Dr. Lindsay Crowshoe from University of Calgary. On behalf of CHRIM I genuinely invite you to enjoy the day and acquaint yourself in these and other exciting new areas of diabetes research.

## from the DREAM Co-Leads

**Dr. Allison Dart** and **Dr. Vern Dolinsky**
Co-Leads, DREAM

Welcome to the 14th annual Diabetes Research Envisioned and Accomplished in Manitoba (DREAM) research symposium, with a theme focused on making connections for innovation. DREAM continues to focus our efforts on translational research to improve the lives of children and families affected by diabetes. We are excited to host four outstanding researchers in diabetes to speak about their research that span the continuum from community-based research to clinical and basic science innovation.

This year, we are pleased to once again partner with MyRoad for the trainee professional development forum on November 12th. This partnership provides a forum for trainees to present their research in an engaging poster session (including 25 poster presentations) and oral presentations selected from the top abstracts. This year we are excited to host 5 external trainees from Toronto and Sherbrooke. Thank you to the Children's Hospital Foundation and Children's Hospital Research Institute of Manitoba (CHRIM) for supporting DREAM, and Toronto Dominion Bank for the generous support for the last 2 years. We'd also like to thank Eli-Lilly, Sanofi, University of Toronto Novo Nordisk Network for Healthy Populations, Research Manitoba and MyRoad for providing funding to make this meeting possible. We are pleased to partner with the Department of Pediatrics on the 12th annual Dr. Heather Dean Lecture in Excellence in Diabetes Research. This year's speaker, Dr. Lindsay Crowshoe will be presenting "Social and Cultural Mechanisms of a Relational Approach to Diabetes Care with Indigenous Patients". We are also going to be acknowledging the important contributions of 3 Knowledge Keepers this year in a Blanket Ceremony led by Elder Jack. We hope that you will enjoy the DREAM symposium!

# Dr. Heather Dean Lecture
## in Excellence in Diabetes

The 14th Annual DREAM Symposium marks the 12th 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.

**Dr. Lindsay Crowshoe**
Associate Professor of Medicine, University of Calgary

# Dr. Lindsay Crowshoe

## "Social and Cultural Mechanisms of a Relational Approach to Diabetes Care with Indigenous Patients"

The objectives of this presentation are to explore elements of culturally safe diabetes care with Indigenous patients, identify key social and cultural contexts as opportunities for supporting patients, and share background research that has generated the above diabetes care approach and discuss next research steps.

Biography:
Lynden (Lindsay) Crowshoe, MD is a Blackfoot primary care physician and researcher, member of the Piikani First Nation and Associate Professor at the University of Calgary Cumming School (CSM) of Medicine. He provides clinical service at the Elbow River Healing Lodge, an Alberta Health Services primary health care clinic for the urban Indigenous population of Calgary that he developed. He focuses on building and sharing knowledge for transforming our health care system to enable best outcomes with Indigenous Peoples through primary health care, system and policy research.

# keynote speakers

## Dr. Barry Lavallee

"Sovereignty: The Real Determinant of Health for First Nations"

**Dr. Barry Lavallee**
Keewatinohk Inniniw Minoayawin Inc.

Barry Lavallee, MD is a member of the Metis community of St. Laurent, Manitoba, and a descendant of Duck Bay and Lake Manitoba First Nations. His research and clinical areas are chronic diseases, transgenerational trauma, impact of colonization on Indigenous communities, and international Indigenous health. Prior to accepting the position of Chief Executive Officer of Keewatinohk Inniniw Minoayawin Inc. in 2020, he practiced Family Medicine in Winnipeg and spent 17 years flying regularly to Tataskweyak First Nation to provide in-community physician services. Throughout his career, he focused on improving care and outcomes for First Nations.

## Dr. Lorraine Lipscombe

"The Network for Healthy Populations: Tackling Diabetes through better care, lower risk factors, and healthier living environments"

**Dr. Lorraine Lipscombe**
University of Toronto

Lorraine Lipscombe, MD is a Professor at the Dalla Lana School of Public Health at the University of Toronto, as well as a clinician scientist and endocrinologist at Women's College Hospital. Dr. Lipscombe leads an internationally recognized research program in diabetes epidemiology and health services, with a particular focus on health services for the management and prevention of diabetes in women. She is also the Executive Director of the University of Toronto's Novo Nordisk Network for Healthy Populations, which is a cross-disciplinary research network that aims to address the burden of diabetes and other chronic diseases.

## Dr. Erin Mulvihill

"Empathy in Action: Making Connections that Drive Innovation"

**Dr. Erin Mulvihill**
University of Ottawa

Erin Mulvihill, PhD is a scientist at the University of Ottawa Heart Institute and an Associate Professor at the University of Ottawa. The Mulvihill Lab studies the actions and regulation of the bioactivity of islet and gut hormones. The lab assesses and carefully measures glucose and lipid metabolism aspects in the context of obesity and type 2 diabetes. Her research program generates and utilizes novel mouse models and experimental models of diabetes and obesity to delineate hormone action mechanisms of direct clinical translational relevance.

# Poster Presentations - Abstract 1

## A Novel Transgenic Inducible GFP Extracellular-Vesicle Reporter Mouse for Isolating Pancreatic Beta-Cell Extracellular Vesicles during Type 1 Diabetes Pathogenesis

**Mystica Amonyi**, Jasmine Pipella, Roozbeh Akbari Motlagh and Peter J. Thompson

**Background/Introduction:** Type 1 diabetes (T1D) is caused by insulin deficiency due to T cell infiltration of islets and beta-(β)-cell destruction. Small extracellular vesicles (EVs) facilitate cellular communication and contain nucleic acids and proteins that may regulate disease progression. While β-cell EVs have been studied from isolated islets ex vivo, the roles they play in vivo in T1D is not known. In vivo studies have been hampered by lack of genetic tools to specifically identify, isolate, and characterize β-cell EVs during T1D pathogenesis.

**Methods:** To gain insight into the relationship between β-cell EVs and their role in the pathogenesis of T1D, we generated a transgenic inducible GFP extracellular-vesicle reporter (TIGER) in the non-obese diabetic (NOD) mouse strain, bearing a Cre-recombinase dependent human CD9-TurboGFP$^{loxP/stop/loxP}$ knocked into the Rosa26 locus. We used an adenoviral-associated vector (AAV)-Ins1-Cre to enable selective TIGER induction in β-cells. We compared diabetes incidence in mice with the TIGER allele, performed immunohistochemistry to confirm specificity of CD9-tGFP to β-cells and isolated EVs produced by cultured islets.

**Results:** NOD.TIGER females and males exhibited similar diabetes spontaneity to wild-type NOD mice (P = 0.6496) and (P = 0.7012), respectively. Immunohistochemistry revealed GFP and Cre expression was specific for β-cells in NOD CD9-TurboGFP$^{TIGER/+}$ micewhen compared to NOD CD9-TurboGFP$^{+/+}$. GFP expression was also observed in a small population of alpha and delta cells suggesting trafficking of β-cell EVs to the cells. Additionally, expression of T-cell marker CD3, was observed within islets prior to diabetes onset. EVs from NOD.TIGER mice revealed similar size distributions and confirmed CD9-tGFP in EVs.

**Conclusion:** This EV reporter NOD mouse model offers a new genetic tool for in vivo labeling pancreatic β-cell EVs, providing insights into their molecular components and trafficking during T1D development.

# Abstract 2

## Investigating how in utero type 2 diabetes exposure affects kidney structure and function in offspring

**Lydia Amooga**, Kristin Hunt, Allison Dart, Pedro Geraldes, and Christine A. Doucette

**Background/Introduction:** Exposure to maternal type 2 diabetes (T2D) has been shown to increase offspring risk for T2D and chronic kidney disease (CKD). However, it is unclear how maternal T2D exposure contributes to the pathophysiological changes in the kidneys of exposed offspring making them more susceptible to CKD. We hypothesized that exposure to maternal T2D impacts fetal development, leading to reduced nephron number, impaired glomerular function and proximal tubular injury in the offspring, increasing susceptibility to CKD.

**Methods:** T2D was induced in female C57BL6 mice prior to pregnancy using diet-induced obesity (8-10 weeks of high-fat and -sucrose (HFS) feeding) and beta cell insufficiency (via injection of 75 mg/kg streptozotocin (STZ)). Control females were fed a chow diet and received a vehicle injection. Control and T2D females were mated with healthy males, and the offspring (males and females) were assessed for various aspects of kidney structure and function at 1- and 3-months of age.

**Results:** Urinary KIM-1 was significantly elevated in T2D-exposed offspring. Fewer glomeruli and thickened glomerular basement membranes without albuminuria were observed in T2D-exposed offspring. Male and female offspring showed similar findings.

**Conclusion:** T2D-exposed offspring experienced mild tubular injury, potentially impacting reabsorption of glucose, water and sodium. While in utero T2D exposure did not cause glomerular damage, the glomerular basement membrane thickening, and reduced number of glomeruli suggest underlying changes that may increase kidney susceptibility to subsequent post-natal stress. Future studies exploring the responsible molecular mechanisms and characterizing how T2D exposure influences kidney function with subsequent post-natal stress are needed.

# Abstract 3

## Enhancing Type 2 Diabetes Prevention Among Young Adults in Peel: Mapping and Understanding Access to Physical Activity and Nutritional Supports

**Carlo Chan**, Matthew Adams, Vanita Varma, Maryam Niapour, Calvin Ke, Ian Zenlea, and Cilia Mejia-Lancheros

**Background/Introduction:** Peel Region of Ontario has a high population of young people aged 20-29, with a Type 2 Diabetes (T2D) prevalence rate 40% higher than the rest of Ontario. T2D among young people remain mostly undetected and understudied. The urban sprawl and predominantly auto-oriented urban environment in Peel limit access to essential resources including healthy food options and recreational resources, which are both crucial to T2D prevention.

**Methods:** Our project aims at identifying the socio-economic factors that affect T2D prevalence among young people in Peel through a community-engaged mixed method approach. First, we mapped out the occurrences of food deserts, food swamps and recreational deserts using GIS mapping. From the resulting maps, we found a loose association between T2D prevalence rate and access to healthy food and physical activity. We then conducted individual interviews with young adults to learn about their lived experience in relation to access to healthy food and physical activity in Peel.

**Results:** From the interviews we found out that there is a cultural underpinning to the obstacles and barriers young people are facing in terms of accessing healthy food and physical activity. In addition, a community advisory board (CAB) was set up, involving various shareholders in the community, including community health centre, food bank, healthy cooking initiative, health researchers and student participants with lived experience. The CAB was invited to discuss the research findings and will be co-designing a GIS-based Story Map with the goal of public education and raising awareness on T2D prevention. The CAB will also help identify areas of concern regarding community resources that support healthy lifestyle.

**Conclusion:** This community engagement approach would help facilitate a meaningful dialogue between service providers and service recipients and address the current challenges in promoting healthy lifestyle as an effective way of T2D prevention among young people.

# Abstract 4

## Meeting the Dual Needs of Hunger & Diabetes: Development of a Food-Bank Based Diabetes Prevention & Management Program

**Jashnoor Chhina**, Liana De Medeiros, Selina Quintenbar, and Vasanti Malik

**Background/Introduction:** In 2025, 25.5% of Canadian households experienced food insecurity, a well-established risk factor for type 2 diabetes (T2D). Peel Region, Ontario, has the country's highest South Asian immigrant population and a T2D prevalence of 15.5%— well above the provincial average of 9.8%. Seva Food Bank, serving over 3,000 Peel families monthly, is uniquely positioned to integrate diabetes prevention into its food education programs. We partnered with Seva to co-design diabetes and nutrition education programming, starting with seniors as a priority group.

**Methods:** We developed a semi-structured focus group guide to explore knowledge of diabetes, barriers to healthy living, and feedback on existing programs. It was applied in an in-person focus group with 9 seniors (6 women, 3 men), all past participants of Seva's cooking program, conducted in English with Punjabi/Hindi translation. Sessions were audio-recorded, transcribed, and inductively coded in NVivo 15 by two reviewers. Additional focus groups with youth and newcomers are scheduled, after which programming will be developed, reviewed with a community working group, and pilot-tested using a pre–post design.

**Results:** Seniors demonstrated a strong awareness of diabetes, often informed by personal or family experience. While they understood the role of diet, exercise, and weight-management, they described key challenges in managing risk: (1) nutrition label confusion (2) barriers to healthy eating (high costs, distance); and (3) knowledge gaps (uncertainty about sugar, oil). For future programming topics, participants emphasized reducing harmful food habits, affordable cooking, and label reading. They emphasized hybrid delivery, digital-literacy support, and take-home resources as prerequisites for equitable education.

**Conclusion:** Despite strong awareness of diabetes, seniors face barriers preventing them from translating knowledge into practice. Addressing these barriers requires not only relevant education but also equitable delivery formats. Through this, food banks can ultimately become frontline partners in closing gaps in diabetes prevention and care.

# Abstract 5

## From Coast to Coast: How Immigration Status Shapes the Risk of Metabolic-Associated Fatty Liver Disease in Canada

**Carlina Colussi**, René Marechal, Jean-Patrice Baillargeon. and Gérard Ngueta

**Background/Introduction:** Metabolic-Associated Fatty Liver Disease (MAFLD) is closely linked to insulin resistance, type 2 diabetes, and other metabolic disorders. Understanding its distribution across population groups is crucial for early prevention. In Canada, immigrants represent a large and diverse segment of the population, and changes in lifestyle and environment after migration may influence their metabolic health. This study aimed to describe the overall and subgroup prevalence of MAFLD in Canada, comparing Canadian-born and immigrant populations, and to explore trends over a twelve-years period.

**Methods:** We analyzed six cycles of the Canadian Health Measures Survey (CHMS), including adults aged 18 and older. Participants were classified by MAFLD status and immigration background (immigrants = born outside Canada; Canadian-born = born in Canada). Weighted analyses accounted for the survey's complex design.

**Results:** Prevalence was higher among Canadian-born than immigrants in cycles 1–4 (27.1–33.7% vs. 26.2–30.8%), but declined thereafter, converging in cycle 6 (27.0% vs. 27.9%). In the weighted logistic regression, all variables included in the model were significantly positive associated with MAFLD. Immigration status was also associated with greater odds (OR=1.093; 95% IC: 1.090-1.096). Older age and higher BMI were linked to increased odds (OR=1.018; 95% IC: 1.018-1.018, and OR=1.139; 95% IC: 1.139-1.139, respectively). Women had a 31 % lower likelihood of MAFLD than men (OR=0.688; 95% IC: 0.686-0.689).

**Conclusion:** MAFLD is prevalent in the Canadian population, although below the estimated global average of 38%. Its occurrence shows associations with age, BMI, and sex. While immigrants showed lower prevalence than Canadian-born individuals in earlier cycles, this difference was smaller in later cycles, reflecting convergence at the group level rather than changes in individual risk. These findings highlight the importance of early prevention strategies for both populations, with particular focus on weight management and age-related risks.

# Abstract 6

## Circadian Clock mutation exacerbates mitochondrial dysfunction and autophagy in diabetic cardiomyopathy

**Molly Crandall**, Victoria Margulets, Huong Nguyen, Inna Rabinovich-Nikitin, and Lorrie Kirshenbaum

**Background/Introduction:** Diabetes mellitus accounts for over five million deaths worldwide with cardiovascular complications affecting more than a third of diabetic patients, including the development of diabetic cardiomyopathy (DCM). Circadian rhythm regulates various physiological processes according to the light/dark cycle and disruption of the circadian clock is a known contributor to type 2 diabetes (T2D) and cardiovascular disease. Reduced insulin sensitivity and impaired beta cell function have been linked to circadian misalignment, suggesting that circadian rhythm plays a role in the development of T2D pathophysiology. Interestingly, the circadian clock also regulates quality control mechanisms and mitochondrial function which is altered in DCM. Therefore, individuals with disrupted circadian rhythm, namely shift workers, may be at greater risk of DCM due to abnormal cellular clearance processes, such as autophagy, and dysfunctional mitochondria.

**Methods:** 3-month-old male C57Bl6/J and CLOCK Δ19/ Δ19, where mutant CLOCK protein inhibits transcription of circadian controlled genes, mice were fed a normal chow or high-fat (60% kcal) diet (HFD) for 8 weeks to induce DCM. Echocardiography assessed cardiac parameters pre- and post-diet. Adult cardiomyocytes were then isolated and infected with GFP-LC3 or MitoKeima encoded adenovirus for epifluorescent microscopy.

**Results:** Body and heart weight were significantly increased with HFD and further elevated in CLOCK Δ19/ Δ19 mice. HFD resulted in abnormal cardiac parameters, including reduced left ventricular internal diameter systole, which worsened with mutated CLOCK. Epifluorescent microscopy revealed that autophagy and mitophagy was significantly elevated with HFD and mutant CLOCK.

**Conclusion:** In conclusion, non-functional CLOCK protein with HFD led to overactive autophagy directed towards mitochondria, suggesting elevated presence of dysfunctional mitochondria. Therefore, circadian misalignment contributes to worsened cardiac state during DCM. As individuals with disrupted circadian rhythms, such as shift workers, have higher risk of T2D, it is essential to reveal the relationship between the circadian clock and DCM for the development of novel therapeutics.

# Abstract 7

## Mental Health Outcomes and Physical Activity in Adolescents with Type 1 Diabetes. A Systematic Review and Meta-analysis with Meta Regression

**Eiva Fallahasady**, Hanna Steiman De Visser, Taelyr Dewarle, Shaelyn Strachan, Brandy Wicklow, Jennifer Yamamoto, and Jon McGavock

**Background/Introduction:** Adolescents living with Type 1 Diabetes (T1D) face daily challenges in balancing insulin, food, and physical activity (PA) which place burden on their mental health. While PA is a cornerstone in fostering positive mental health in adolescents, there is a surprising absence of empirical evidence for the role of PA in supporting the mental health of adolescents living with T1D. Therefore, the aim of this systematic review and meta-analysis with meta-regression is to synthesize all previous studies and research to test for (1) differences in mental health between adolescents with T1D peers without diabetes and (2) potential mediating effects of PA and mental health outcome in adolescents living with T1D.

**Methods:** We will search CINAHL, EMBASE, MEDLINE, SPORTDiscus and PsycINFO for the published articles and Google Scholar, ProQuest Dissertation & theses comparing mental health outcomes between adolescents with T1D and controls without T1D. We will include observational studies with at least one measurement of mental health outcome in children and adolescents aged 10 to 18 with T1D and control groups. The risk of bias will be assessed by Newcastle-Ottawa and for the quality of evidence, we will use GRADE methodology. Data extraction will be done with two reviewers. If meta-analysis is possible, the effect size and pooled random-effects model will be calculated. We will conduct meta-regression analysis for finding potential mediator including PA, sex, mean age, study design and mental health outcome type. Results of search and preliminary study demographics will be presented at the meeting.

**Conclusion:** This systematic review will provide valuable insights into (1) the prevalence of mental health outcomes and (2) the potential role of PA is fostering positive mental health factors in adolescents with T1D. These results could potentially inform clinical practice and interventional studies to improve youth living with T1D mental health with PA.

# Abstract 8

## Effect of Protected Cycling Trail on Active Transportation, Physical Activity and Cycling Traffic: A Natural Experiment

**Isaak Fast**, Nika Klaprat, Todd Duhamel, and Jonathan McGavock

**Background/Introduction:** Physical activity (PA) in childhood is a critical determinant of lifelong health, yet over 60% of Canadian children do not achieve the recommended 60 minutes of daily PA. Despite significant municipal investments in cycling infrastructure, there is little evidence on their impact on youth PA. We will eventually test the hypothesis that children living within 600 metres (m) of a new multi-use trail will experience increases in cycling traffic, cycling commuting to school, compared to control neighbourhoods using a type 1 hybrid-effectiveness implementation design. Here we present baseline data prior to the construction and opening of the new trail.

**Methods:** In partnership with the City of Selkirk, we designed a natural experiment consisting of a new 3-km protected multi-use trail. Six schools located within 600m of the trail are considered “exposed” to the new trail and three schools, beyond 600m are considered “unexposed.” The two primary outcomes are (1) commuting to school via bicycle and (2) overall cycling traffic. From May 2024 to June 2025, we counted bicycles parked at each school for 15-days to calculate daily cycle commuting rates at each school relative to school enrollment. Automated Eco-counters embedded in the trail provide continuous hourly cycling traffic data from May 2024 to September 2025.

**Results:** Across pre-intervention observations, intervention schools experienced 5.8 (95% CI: 5.3-6.4) bikes parked/day, which corresponds to a 2.6% cycling-to-school rate for students enrolled at the schools. Conversely, control schools averaged 2.2 (95% CI: 1.9-2.6) bikes per day, which corresponds to a cycling-to-school rate of 1.4%. Both intervention and control neighbourhoods show parallel trends—a vital assumption of difference-in-differences analysis. Daily cycling traffic along the road where the trail is being installed was 43.5 (05% CI: 37.2-49.9) counts/day.

**Conclusion:** This study is the first natural experiment in Canada to rigorously evaluate the effects of the addition of significant cycling infrastructure on active transportation to schools. Baseline data suggest that rates of cycling are very low suggesting that changes following a new trail are potentially detectable.

# Abstract 9

## North American Pediatric Endocrinologist Perspectives on Implementation of the iCARE eGFR Equation for Screening for Diabetic Kidney Disease in Youth with Type 2 Diabetes

**Giliana P. Garcia Acevedo**, Allison B. Dart, Elizabeth A. C. Sellers, Valerie Umaefulam, and Brandy A. Wicklow

**Background/Introduction:** The iCARE estimated glomerular filtration rate (eGFR) equation has been developed and validated as the most accurate estimate of kidney function in youth living with Type 2 diabetes (T2D). If implemented in addition to urine protein screening for diabetic kidney disease (DKD), it could provide further understanding about the DKD disease course and monitor the effects of treatment. Our study aimed to explore pediatric endocrinologists' perspectives on the barriers and facilitators to implementation of the iCARE equation into routine care for youth with T2D.

**Methods:** A qualitative study was conducted and data obtained via focus groups with pediatric endocrinologists in North America utilizing a semi-structured focus group guide informed by the Consolidated Framework for Implementation Research (CFIR). A thematic analysis was done with a combination of inductive and deductive approaches.

**Results:** Four focus groups were conducted (two with Canadian providers and two with United States providers representing 8 centres). Major barriers to implementation of the iCARE eGFR were 1) the evidence base available for its use, 2) unknown generalizability to other regions and populations, and 3) unknown impact on patient outcomes. Another barrier was participants' uncertainty in interpretation of the eGFR results. Facilitators for implementation discussed were technology strategies such as incorporation of the iCARE eGFR into Electronic Medical Records (EMRs) and development of an application or a website. Guideline integration was also endorsed as a significant facilitator. Pilot studies were seen as a valuable next step for implementation in clinical settings, as well as longitudinal studies to assess predictive value of eGFR in childhood and CKD progression.

**Conclusion:** Successful implementation of the iCARE eGFR will require continued validation and external validation studies, as well as technology efforts to support interpretation and use. Pilot studies will provide data on iCARE eGFR uptake by diabetes providers.

# Abstract 10

## The Impact of Diet-Induced Obesity on Myeloid Cell Metabolism in Mice

**Floriane Houenagnon**, Danish Malhotra, and Samantha Pauls

**Background/Introduction:** Obesity is associated with low-grade chronic inflammation that contributes to the development of type 2 diabetes mellitus (T2DM). Monocytes and macrophages drive this inflammation, and their function is linked to metabolic pathways such as mitochondrial respiration. In humans with obesity and T2DM, circulating myeloid cells show elevated glucose-driven respiration. Whether similar changes occur in mouse myeloid cells remains unclear.

**Methods:** To address this, C57BL/6J mice were fed either low-fat sucrose (LFS; 10% kcal fat, 3.5% sucrose) or high-fat sucrose (HFS; 45% kcal fat, 17% sucrose) diets for 13 weeks. Body weight and glucose tolerance were monitored for all mice (n=8 male and n=12 female per diet group). Bone marrow was harvested to isolate monocytes and generate macrophages. Mitochondrial respiration was successfully measured by Seahorse XFe24 analysis for a subgroup of mice. Cytokine levels in bone marrow extracellular fluid were quantified by a Luminex multiplex assay.

**Results:** HFS feeding led to weight gain and impaired glucose clearance. Statistical analysis with sexes combined (n=7-13 diet group) showed no difference in macrophage or monocyte respiration between LFS and HFS. Interim cytokine analysis of bone marrow extracellular fluid revealed that interleukin-6 was elevated in LFS females versus LFS males and HFS females ($p<0.05$). Interleukin 1-β and monocyte chemoattractant protein 1 were higher in males compared to females ($p<0.05$).

**Conclusion:** Our findings suggest no differences in macrophage or monocyte respiration between LFS and HFS diets. Monocyte respiration analysis was limited by a lack of technical replicates. Cytokine results suggest sex- and diet-dependent changes in the bone marrow microenvironment.

# Abstract 11

## The Endothelial Cell Response to Docosahexaenoic Acid is Growth State-Dependent: An RNA-seq Study

**Shiqi Huang**, Peter Zahradka, and Carla G. Taylor

**Background/Introduction:** Endothelial cells play an essential role in maintaining the homeostasis of the cardiovascular system. Endothelial dysfunction, characterized by alterations in endothelial nitric oxide synthase (eNOS) activity, can lead to atherosclerosis, the most common complication of diabetes. Omega-3 fatty acids are deemed athero-protective, but the effects of docosahexaenoic acid (DHA) remain contentious. We found DHA differentially activates eNOS in growing versus quiescent endothelial cells, which may approximate the dysfunctional and healthy endothelium, respectively. Therefore, we hypothesized that DHA would benefit quiescent, but not dysfunctional endothelial cells.

**Methods:** Human EA.hy926 endothelial cells treated with DHA (0, 20 or 125 μM for 8 h) in the 2 distinct growth states were analyzed by RNA-seq. Differentially expressed genes (DEGs) related to the top 5 enriched pathways were validated by RT-qPCR and/or Western blotting. Cellular cholesterol content and eNOS mRNA stability were tested.

**Results:** The transcriptomic profiles showed distinct groupings based on cell growth state and DHA concentration. The top 5 enriched pathways from DESeq2-identified DEGs included 4 steroid metabolism pathways, particularly cholesterol biosynthesis. HMGCR, SREBF2, and INSIG1 were downregulated in quiescent cells only by 20 μM DHA, while SREBF1 was downregulated in both states. DHA at 20 μM also reduced cellular cholesterol content, similar to atorvastatin, in quiescent cells only. Moreover, Rho GTPase pathway genes, downstream of HMG CoA reductase, were downregulated by 20 μM DHA only in quiescent cells. At the protein level, RhoB, but not RhoA or RhoC, responded to DHA. NOS3 mRNA stability, which is affected by Rho GTPases, was improved by DHA.

**Conclusion:** Our study reveals that DHA context-dependently affects endothelial cells through multiple pathways, and only quiescent endothelial cells respond positively to DHA. Future clinical trials with DHA should take subjects' endothelial health into consideration, and resolve the athero-prevention-versus-treatment effects of DHA, especially for cardiovascular management in diabetes.

# Abstract 12

## First Nations youth and family engagement in youth-onset type 2 diabetes research: The iCARE cohort

**Brianna Hunt**, Elizabeth Sellers, Jon McGavock, Michelle Roy, Jackie McKee, Jennifer Lopez, Brandy Wicklow, and Allison Dart

**Background/Introduction:** In Manitoba, rates of youth-onset type 2 diabetes (T2D) are the highest in the world, with First Nations youth being disproportionally affected. Established in 2012, improving renal Complications in Adolescents with T2D through REsearch (iCARE) is the largest cohort study of youth with T2D inCanada, focused on wholistic understandings of kidney disease as a complication of youth-onset T2D. Meaningful collaboration between First Nations youth and families, health researchers, and clinical practitioners is essential to address ongoing health inequities resulting from policies and practices that systemically and systematically disadvantage First Nations.

**Methods:** Since 2015 the iCARE research team has included a group of young people living with T2D, family, and community members known as the iCARE Participant and Family Advisory Group (PAG). This group meets quarterly, ensuring that iCARE research priorities, hypotheses, methods, analyses, interpretation, and knowledge mobilization are relevant to First Nations youth and families. This collective is characterized by meaningful relationships, power sharing, and reciprocal collaboration.

**Results:** This poster showcases key project priorities guided by the PAG, changes in project direction, and knowledge mobilization materials co-created by the iCARE PAG. A key patient priority of the PAG has been the importance of stress and mental health as a crucial comorbidity impacting outcomes of youth-onset T2D. This priority led to the implementation of a pilot mental health skills program (Dialectical Behavioral Therapy) to support youth living with T2D.

**Conclusions:** The ongoing success of the iCARE cohort study and the associated projects and findings is in large part due to the meaningful and reciprocal research partnership with the PAG. Ongoing health inequities reflect the universal need for meaningful youth, family, and community engagement, and the iCARE PAG model serves as replicable model for application across other health and basic science research programs.

# Abstract 13

## Resveratrol as bread ingredient for improving starch digestibility and glycemic potential

**Sunita Karki**, Nicola Gasparre, Thomas Netticadan, and Cristina M. Rosell

**Background/Introduction:** Resveratrol (RSV) is a polyphenol with proven pre-clinical and clinical anti-diabetic effects. Also, polyphenols have the potential to inhibit alpha-amylase, an enzyme that breaks down starch into sugar. Alpha-amylase inhibition helps in regulating blood sugar levels by controlling starch digestion and thereby prevent hyperglycemia. While RSV is mainly available as nutraceutical supplement, incorporating it into staple foods like bread could provide broader, accessible health benefits. Hence, this study evaluated whether RSV fortification in bread could modulate starch digestion.

**Methods:** White bread (WB) and whole wheat bread (WWB) were prepared by incorporating 0.5 g RSV/100 g flour. In vitro starch digestibility was assessed using two complementary methods: enzymatic hydrolysis and Rapid Visco Analyzer (RVA) digestograms. Key parameters included rapidly digestible starch (RDS), slowly digestible starch (SDS), resistant starch (RS), and total digestible starch (DS), digestion rate (k). RSV recovery and bread quality attributes (color and texture) were also analyzed.

**Results:** In WB, RSV incorporation significantly ($p<0.05$) reduced RDS from 51.47% to 29.91%, increased SDS from 39.59% to 55.40%, and enhanced RS from 10.93% to 12.69%. Regarding k, nearly 50% reduction was found compared to breads without RSV. RVA profiles supported these findings. In WWB, RSV significantly ($p>0.05$) reduced RDS (from 45.6% to 31.08%) but showed no significant changes in SDS or RS. RSV recovery was 41.11% in WB and 29.82% in WWB. Importantly, bread color and texture were not significantly affected in the both types of bread.

**Conclusion:** RSV fortification of bread significantly altered starch digestibility, particularly in white bread, by lowering RDS and increasing SDS and RS. These effects suggest reduced postprandial glycemic potential without compromising product quality. With substantial RSV recovery, bread could be feasible, accessible, and cost-effective vehicle for RSV delivery. This strategy highlights the potential of functional daily diet for improving glycemic control and supporting diabetes prevention and management.

# Abstract 14

## Sex Differences in Autophagy Regulation in Cardiometabolic Syndrome Induced Heart Failure

**Charlotte Kowall**, Huong Nguyen, Ruzzell Flores, Molly Crandall, Inna Rabinovich-Nikitin, and Lorrie Kirshenbaum

**Background/Introduction:** Heart failure with preserved ejection fraction (HFpEF) is rising in Canada and has been linked to cardiometabolic syndrome, which is a known contributor to type-2 diabetes. Additionally, patients suffering from diabetic cardiomyopathy may develop HFpEF. Interestingly, for reasons unknown, the incidence and severity of HFpEF tracks differently in females and males. Recent studies from our laboratory have identified autophagy, which is critical for maintaining cell viability and cardiac function, as being regulated differently in females and males. Herein, we explore the possibility that sex specific differences in autophagy underlie the severity of HFpEF in cardiometabolic disease.

**Methods:** For these studies, we used a well- established 'two-hit' mouse model of cardiometabolic syndrome to induce HFpEF. C57B6/J mice were fed either normal chow diet or a high fat diet (>60% fat) in the absence and presence of L-NAME in drinking water for 5 weeks. Cardiac functional end-points including non-invasive echocardiography, blood pressure, and weight measurements were assessed serially in mice along with qPCR and Western blot analysis on mice hearts.

**Results:** In contrast to male mice, we observed a marked increase in autophagy markers Bnip3, LC3II and reduction of p62 in the hearts of female mice fed HFD in the presence of L-NAME - indicative of increased autophagy and autophagic clearance compared to male cohorts. Further, these changes in autophagy activity corresponded with improved functional parameters including fractional shortening (FS) and left ventricular internal diameter (LVID) in female mice compared to males.

**Conclusion:** The findings of the present study reveal a mechanistic link between autophagy and sex specific differences in cardiometabolic syndrome that may account for the development and severity of HFpEF associated with cardiometabolic disease. Consequently, therapeutic interventions designed to modulate cellular quality control mechanisms, like autophagy, may prove beneficial in mitigating sex specific differences in individuals with cardiometabolic syndrome.

# Abstract 15

## New Apelinergic Analogues Rescue Blood Flow Perfusion and Sensory Function in Diabetic Hind Limb Ischemia

**Marie-Sophie Lachance**, Pierre-Luc Boudreault, Philippe Sarret, and Pedro Geraldes

**Background/Introduction:** Diabetic peripheral artery disease (PAD) is characterized by impaired new blood vessel formation following ischemia, leading to high amputation risk. Although experimental pro-angiogenic therapies such as VEGF delivery have been explored, clinical outcomes remain limited. Our group has reported that apelin perfusion treatment could improve blood reperfusion in the ischemic muscle of diabetic mice. However, apelin's poor plasma stability limits its therapeutic utility. To address this, we have investigated the effects of plasma-stable apelinergic analogs (KT04-44 and AM03-68) on endothelial cell (EC) function and blood reperfusion in a diabetic hindlimb ischemia model.

**Methods:** Primary ECs were exposed to normal (5,6 mM) or high glucose (25 mM) concentrations for 48h and hypoxia (16h). EC signaling and function (proliferation, migration, and tube formation) were assessed following stimulation with analogs. Femoral artery ligation was performed in type 1 diabetic mice, and analogs were administered subcutaneously every other day for 4 weeks. Blood flow reperfusion was monitored weekly (laser Doppler). Motor capacity (voluntary wheel), mechanical (von Frey), and thermal (acetone drop) threshold were evaluated.

**Results:** Both apelinergic analogs stimulated EC proliferation, migration (2-fold), and tube formation (2.5-fold) when exposed to normal and high glucose levels. Nondiabetic mice displayed 75% blood flow reperfusion compared to 38% in diabetic mice. Diabetic mice treated with KT04-44 and AM03-68 had 81% and 75% recovery, respectively. Motor capacity and pain threshold both altered in diabetic, were improved in treated diabetic mice. VEGF-A, APLNR, and PDGF-B mRNA expression recovered with the analog treatment. Muscle fiber diameter and arteriole count were preserved in both treated diabetic mice compared to non-treated.

**Conclusion:** Local injection of apelinergic analogs rescues blood flow reperfusion, improves endothelial function, and preserves sensory capacity in diabetic mice. These analogues represent promising therapeutic candidates for reducing amputation risk and improving quality of life in patients with diabetic PAD.

# Abstract 16

## High Nutrient Load Induced Immune Cell Activation: Implications in Type 2 Diabetes and Obesity

**Danish Malhotra**, Floriane Houenagnon, and Samantha Pauls

**Background/Introduction:** Chronic, low-grade inflammation is a driving factor in metabolic diseases like obesity and type 2 diabetes. Immune cells, especially monocytes and macrophages, contribute by releasing pro-inflammatory cytokines. The underlying mechanism(s) regulating immune cell activation in metabolic disorders remain poorly understood. Bacterial lipopolysaccharide (LPS) is the most common pro-inflammatory trigger used to study innate immune activation; however, it is a poor model for metabolic inflammation in vivo.

**Objective:** To investigate the effects of physiologically relevant stimuli: nutrient overload (glucose-palmitic acid) and TNF-α (secreted by hypertrophic adipocytes) on innate immune cells.

**Methods:** THP-1 monocytes were preconditioned in basal glucose (5 mM) for 48h and then treated with: High glucose (15mM) plus palmitic acid (500μM) or TNF-α (5-25ng/mL), alone or in combination for 24h. In some experiments, cells were pre-treated with docosahexaenoic acid (DHA; 40μM). Supernatants were analyzed for interleukin-1β (IL-1β) by ELISA. Transcript levels of TLR4, IL-1β and CCL2 were measured by qPCR. Mouse bone marrow–derived macrophages (BMDMs) were similarly treated with high glucose (25mM) plus palmitic acid (500μM), and supernatants were assessed for IL-6 secretion by ELISA.

**Results:** THP-1 monocytes exposed to high glucose and palmitic acid showed increased IL-1β secretion relative to control treatment, which was further amplified by co-stimulation with low-dose TNF-α. Preliminary qPCR results indicated upregulation of IL-1β and CCL2 transcripts. DHA pre-treatment markedly reduced cytokine release. Furthermore, BMDMs treated with high glucose-palmitic acid did not exhibit detectable IL-6 secretion in either control or stimulated conditions.

**Conclusion:** High nutrient conditions triggered strong pro-inflammatory responses in THP-1 monocytes, which were attenuated by DHA, indicating its therapeutic potential. Further cytokine profiling in BMDMs is ongoing. The establishment of a relevant in-vitro model of innate immune activation by nutrient excess will lay the foundation for mechanistic investigation into how inflammation is regulated by DHA and other interventional agents.

# Abstract 17

## Muscle-restricted SIRT3 Overexpression Protects Against Gestational Diabetes-Induced Cardiac and Metabolic Dysfunction in Offspring in a Sex-Specific Manner

**Caitlin Menzies**, Mateusz M Tomczyk, Bo Xiang, Stephanie M. Kereliuk, Richard Leduc, and Vernon W. Dolinsky

**Introduction/Background:** Intrauterine exposure to maternal gestational diabetes mellitus (GDM) increases cardiovascular risk in offspring later in life, yet the mechanisms remain unclear. In rodents, GDM induces cardiac hypertrophy and aberrant mitochondrial protein acetylation, coinciding with reduced expression of the mitochondrial deacetylase Sirtuin-3 (SIRT3). The objective of this study is to define the role of SIRT3 in GDM-induced cardiac dysfunction and to investigate its potential as a therapeutic target.

**Methods:** GDM was induced by feeding female mice a HFS diet (45% fat) for 6 weeks prior to mating. Control dams were fed a low-fat (LF; 10% fat) diet. Dams were mated to transgenic (TG) male sires overexpressing SIRT3 under the muscle-creatine kinase promoter, generating litters with both SIRT3-TG and non-TG offspring. Post-weaning, offspring were placed on LF or HFS diets. At 15 weeks cardiometabolic function was assessed via echocardiography.

**Results:** Non-TG offspring exposed to GDM and postnatal HFS diet (GDM-HFS) displayed cardiac hypertrophy in both males (Left Ventricular (LV) mass, non-TG GDM-HFS vs non-TG Lean-LF, $p<0.001$) and females (LV wall thickness non-TG GDM-HFS vs non-TG Lean-LF, $p<0.05$), which was absent in SIRT3-TG offspring. GDM exposure altered acetylation of mitochondrial peptides in non-TG male offspring and was exacerbated by a postnatal HFS diet (GDM-HF vs Lean-LF 88 peptides, $p<0.05$). Functional classification revealed prominent representation of acetylated proteins in fatty acid oxidation, respiratory electron transport, and mitochondrial biogenesis in hearts of GDM-exposed offspring.

**Conclusion:** SIRT3 overexpression protects against GDM- and HFS diet-induced cardiac hypertrophy in both male and female offspring. Acetylomics also identifies cardiac mitochondrial protein acetylation as a potential mechanism that induces GDM- and HFS-induced cardiac abnormalities. These findings highlight the importance of SIRT3 in mediating the effects of GDM on the heart and support SIRT3 as a potential therapeutic target.

# Abstract 18

## SIRT3 Deficiency in the Liver Results in Hepatic Steatosis and Elevated Circulating Lipids in Gestational Diabetes

**Jewel Paskaruk**, Khushali Trivedi, Bo Xiang, and Vernon Dolinsky

**Background/Introduction:** Gestational diabetes mellitus (GDM) is the most common pregnancy complication, affecting around 5-10% of pregnancies at the time of delivery in Canada, with obesity being a major risk factor. Adaptations to pregnancy require a shift from glucose to fat utilization for energy. Fat accumulation in the liver contributes to insulin resistance, which is characteristic of GDM. This project investigates the role of Sirtuin 3 (SIRT3), a mitochondrial protein deacetylase that regulates energy pathways such as fatty acid oxidation during pregnancy.

**Hypothesis:** SIRT3 deficiency in the liver induces hepatic steatosis and elevated circulating lipids during pregnancy.

**Methods:** Mice with liver-specific-deletion of SIRT3 (SIRT3-LKO) were generated by crossing $Sirt3^{tm1.1Auw}$ mice from Jackson Labs with albumin-promoter driven cre-recombinase mice. SIRT3-LKO mice and controls were fed either low fat diet (10% kcal fat) or high fat sucrose diet (45% kcal fat) for 6-weeks before pregnancy and throughout the 3-week mouse pregnancy to induce GDM. Pregnant mice were sacrificed at gestational day 18.5. Lipids were histologically visualized in liver using Oil Red O. Serum and liver lipids were measured biochemically.

**Results:** SIRT3-LKO mice exhibited significant hepatic steatosis during pregnancy, as indicated by a 2-fold increase in Oil Red O positive area of stained liver sections ($p<0.0001$) and a 1.8-fold increase in hepatic triglyceride concentration ($p<0.05$) compared to control mice. Serum triglyceride and free fatty acid concentrations were elevated by 1.4-fold ($p<0.01$) and 2-fold ($p<0.05$), respectively, in the pregnant SIRT3-LKO mice compared to controls.

**Conclusion:** Our results reveal that loss of SIRT3 in the liver during pregnancy leads to hepatic steatosis and dyslipidemia. These alterations in lipid handling are likely to exacerbate liver insulin resistance and glucose intolerance, which are metabolic hallmarks of GDM. These findings suggest that SIRT3 regulates liver lipid metabolism during pregnancy and could be a therapeutic target.

# Abstract 19

## Exploring the role of beta cell stress gene p21 in type 1 diabetes

**Camille Prefontaine**, Jasmine Pipella, Mystica Amonyi, and Peter J. Thompson

**Background/Introduction:** During the progression of type 1 diabetes (T1D), senescent β-cells accumulate and contribute to disease pathogenesis. Cellular senescence is a state of irreversible cell cycle arrest and suppression of apoptosis. Which pathway controls the senescence entry in β-cells in T1D has not been determined. Current evidence strongly suggests a role for the p53/p21 pathway in senescence during T1D development in the nonobese diabetic (NOD) mouse model and human β-cells from T1D donors. We hypothesized that p21 controls the activation of the senescence phenotype in T1D, and deletion of the gene encoding p21 (Cdkn1a) in β-cells will prevent senescence phenotypes and delay T1D onset in the NOD mouse model.

**Methods:** The Thompson lab generated a novel conditional knockout allele for Cdkn1a on the T1D-prone NOD/ShiLtJ strain. Adeno-associated virus 8 (AAV8) containing the Cre recombinase under the control of the rat Ins1 promoter (AAV8-Ins1-Cre) was used to induce the Cdkn1a knockout. Mice were intraperitoneally injected with AAV8 at 6 weeks of age. Blood glucose was measured weekly for 30 weeks to determine the spontaneous diabetes incidence in male and female Cdkn1a$^{flox/+}$ NOD mice compared to controls.

**Results:** Diabetes incidence remained unchanged in the Cdkn1a$^{flox/+}$ AAV8-injected group in comparison to the Cdkn1a$^{flox/+}$ PBS-injected control group, in both males ($p=0.492$) and females ($p=0.130$). Additionally, there were no significant differences in random blood glucose levels or body weight. These findings are consistent with Cdkn1a haplosufficiency, as only a single allele is sufficient for normal function.

**Conclusion:** T1D is a growing health concern in Manitoba that involves the loss and impairment of β-cell function. While it is known that senescent β-cells accumulate during the pathogenesis of diabetes, the pathway controlling the entry into senescence is still undetermined. This project provides further insights into the role of p21 in β-cell senescence and diabetes pathogenesis.

# Abstract 20

## Extracellular vesicle release with acute electrical pulse stimulation in skeletal muscle is AMPK-dependent

**Hans Sanchez**, Nicholas Klassen, Hashini Chandrasena, Tamiris de Fatima Goebel de Souza, Patience O. Obi, Berkay Özerkliğ, and Ayesha Saleem

**Background/Introduction:** Extracellular vesicles (EVs) are membrane-bound nanoparticles secreted by all cells, and carry bioactive cargo that can alter cell function. We previously demonstrated that chronic electric pulse stimulation (EPS) of myotubes enhanced EV release, and that these EVs evoked mitochondrial biogenesis in other myocytes. Increased mitochondrial biogenesis is linked with improved insulin sensitivity, which underscores further investigation into the pro-metabolic effect of EVs. Here we sought to elucidate the underlying mechanisms regulating EV secretion with EPS. Given that AMP-activated protein kinase (AMPK) is activated with muscle contraction, we hypothesized that EPS will increase EV secretion via AMPK.

**Methods:** Mouse muscle cells were differentiated into myotubes (N=7), and subjected to acute EPS (3hrs @14V, C-PACE EM, IonOptix). A separate set of EPS experiments were done with, or without AMPK inhibitor, Compound C (0, 5, 10μM; N=4). Unstimulated myotubes were used as controls. EVs were isolated from conditioned media, and characterized using single-particle analysis. Cells were examined under a microscope for morphological changes, assessed for changes in protein concentration/yield using BCA assay, and protein expression (AMPK phosphorylation, cellular stress markers such as HMGB1, AIF, and HSP70) using immunoblotting. Data were analysed using t-tests, RM one-way, or two-way ANOVAs.

**Results:** Acute EPS led to a 2.2-fold increase in EV concentration ($p=0.0045$), and size distribution analysis showed higher EV concentration at all sizes (~50-200nm, $p=0.0006$) vs. control. Average EV size (~110nm) was unaffected with EPS. Treatment with 10μM of Compound C ameliorated the EPS-induced ~2-fold increase in EV secretion ($p=0.0197$) to control levels. No changes in cell morphology, and total protein yield between treatments were observed. Likewise, protein expression levels of HMGB1, AIF, and HSP70 remained unchanged. AMPK phosphorylation validation of results is in progress.

**Conclusion:** Our data demonstrate that acute EPS enhances EV secretion in an AMPK-dependent manner, highlighting a novel putative regulatory mechanism controlling EV secretion.

# Abstract 21

## Optimizing an experimental model of pregestational type 2 diabetes in the HNF-1α-G319S background

**Corey Sanderson**, Kristin L. Hunt, and Christine A. Doucette

**Introduction/Background:** Youth-onset type 2 diabetes (T2D) is rising rapidly, disproportionately affecting Indigenous populations in Manitoba. While it has been established that exposure to T2D in utero markedly increases the risk for youth-onset T2D in the offspring, a gene variant (HNF-1α-G319S) identified in Anishininew communities, also strongly associates with youth-onset T2D. Currently, we have little mechanistic understanding of how the HNF-1α-G319S variant and in utero T2D diabetes exposure interact to influence offspring metabolic health.

**Methods:** We first sought to optimize a model of in utero T2D in heterozygous female HNF-1α-G319S-expressing mice (G/S). To induce insulin resistance, we tested different lengths of high-fat and -sucrose (HFS) diet feeding (6- and 8-weeks) in G/S female mice. To subsequently induce insulin insufficiency, we tested mild doses of streptozotocin (STZ; 50 or 75 mg/kg, i.p.), a drug known to specifically kill beta cells. Bodt weight was measured weekly throughout the study, fasted blood glucose and glucose tolerance tests were performed 1-week before STZ injection and again 2-weeks after STZ injection.

**Results:** 6- and 8-weeks of HFS diet alone significantly impaired glucose tolerance in female G/S mice, with significantly elevated glycemia at 15–60 min vs. chow (Bonferroni-adjusted $p < 0.05$). Subsequent injection of 50mg/kg STZ resulted in greater glucose intolerance, but fasting blood glucose was not significantly elevated in any group.

**Conclusion:** While glucose intolerance was achieved, HFS diet (6- or 8-weeks) combined with low-dose STZ (50 mg/kg) in a G/S background was not sufficient to drive overt T2D. We will continue to test higher doses of STZ to create greater beta cell insufficiency and ultimately fasting hyperglycemia. Once optimized, G/S female mice with T2D will be bred with healthy G/S males to determine how these two factors interact to influence offspring metabolic health, providing valuable insight into potential pathological mechanisms of T2D in indigenous youth.

# Abstract 22

## Treatment with an Interleukin-1 Receptor Antagonist Reduces Formation of Toxic Islet Amyloid Polypeptide Oligomers and Improves Beta-Cell Survival in Human Islets

**Janessa Sawatzky**, Rushie Tyagi, and Lucy Marzban

**Introduction/Background:** Type 2 diabetes (T2D) is associated with beta-cell dysfunction and death, which leads to elevated blood glucose levels. Formation of toxic protein aggregates named amyloid in the pancreatic islets, due to aggregation of the beta-cell hormone human islet amyloid polypeptide (hIAPP), plays a key role in beta-cell death during T2D, but the underlying mechanisms are not clear. Small hIAPP aggregates (oligomers) that form at early stages of amyloid formation are the major toxic form which promote islet IL-1beta production, activation of the IL-1beta signaling, and beta-cell apoptosis. We examined if treatment with an IL-1 receptor antagonist (IL-1Ra) can reduce hIAPP oligomers and amyloid toxicity in human islets.

**Methods:** Isolated human islets from cadaveric donors (n=3) were cultured at normal glucose (5.5 mM; no or little amyloid formation) or elevated glucose (11.1 mM; amyloid formation) in the absence or presence of an IL-1 receptor antagonist (IL-1Ra; 10 µg/mL) for 7 days (37ᵃC). Islets were fixed in 4% paraformaldehyde and paraffin-embedded islet sections were used for assessment of hIAPP oligomers and beta-cell apoptosis, by quantitative immunolabelling for insulin and A11 (oligomer), insulin and TUNEL (or caspase-3), respectively.

**Results:** Pre-culture human islets had little or no detectable hIAPP oligomers, but hIAPP aggregation progressively occurred during 7-day islet culture at elevated glucose, which was associated with increased number of caspase-3 and TUNEL-positive beta cells. Treatment with IL-1Ra reduced formation of hIAPP oligomers in human islets during 7-day culture at elevated glucose, which was associated with lower number of caspase-3 and apoptotic beta cells as compared to non-treated islets cultured at elevated glucose.

**Conclusion:** These findings suggest that IL-1Ra treatment reduces formation of hIAPP oligomers and beta-cell death in human islets. Treatment with IL-1Ra at early stages of amyloid formation may provide an effective strategy to protect islets from beta-cell toxic hIAPP oligomers.

# Abstract 23

## Metabolic Reprogramming In Senescent Beta Cells In Type 1 Diabetes

**Aimeen Sharoze**, Jasmine Pipella, Gabriel Brawerman, and Peter Thompson

**Background/Introduction:** Type 1 diabetes (T1D) results from autoimmune destruction of pancreatic beta cells. In addition to cell death, beta cell stress and senescence are now recognized as contributors to disease progression. Our lab previously showed that DNA damage can drive senescence in beta cells, but how senescence impacts beta cell metabolism is not well understood. We hypothesize that senescence impairs β cell metabolism by dysregulating insulin secretion and disrupting mitochondrial respiration in response to glucose.

**Methods:** Human donor islets were induced into senescence and validated by senescence markers. Glucose-stimulated insulin secretion (GSIS) was measured using static assays and will be further monitored by perifusion with an ultrasensitive HTRF insulin assay or ELISA. Mitochondrial respiration and glycolytic activity will be assessed by Seahorse extracellular flux analysis. Senescent and control β cells will be sorted by flow cytometry for RNA sequencing. Statistical analysis will be performed using one-way ANOVA or unpaired two-tailed t-tests in GraphPad Prism. In preliminary experiments, GSIS was evaluated by static assay in human islets, while mitochondrial membrane potential and biogenesis were assessed in mouse MIN6 and NIT1 β cell lines following senescence induction. To explore transcriptional changes, published RNA-seq datasets comparing control and senescent human islets will be analyzed.

**Results:** Preliminary findings from static assays suggest that senescent β cells exhibit sustained second-phase insulin secretion and continue producing mature insulin in response to glucose. Senescence was also associated with altered mitochondrial membrane potential and biogenesis in MIN6 and NIT1 cells. Transcriptomic analyses support metabolic reprogramming, showing upregulation of stress pathways and mitochondrial quality-control genes such as SPATA18, as well as other genes related to mitochondrial function including GDF15, PRODH, FDXR, and BAX.

**Conclusion:** These studies suggest that senescence drives metabolic changes in beta cells that impair their function. Understanding this reprogramming may provide insight into T1D progression and help identify new therapeutic strategies to preserve beta cell function.

# Abstract 24

## Culturally Appropriate Self-Management Education and Support for Cardiometabolic Disease Prevention in Peel Region: A Community-Engaged Approach

**Amrit Thandi**, Joyeuse Senga, Tharsan Kanagalingam, Sebrin Sharif, Prathiga Suthanthirarajan, David Campbell, Kelly Smith, Lorraine Lipscombe, Raj Pannu, and Calvin Ke

**Background/Introduction:** Diabetes and other cardiometabolic diseases disproportionately affect racialized communities in Canada. Self-management education and support (SMES) programs are critical, but conventional approaches are resource-intensive and fail to address cultural needs. However, barriers and facilitators to SMES among local Punjabi, Tamil, and Afro-Caribbean communities are unclear.

**Methods:** We engaged adults ≥40 years with type 2 diabetes, coronary artery disease, stroke, chronic kidney disease, heart failure, or ≥2 cardiometabolic risk factors, identifying as Punjabi, Tamil, or Afro-Caribbean, and living in Peel Region or Toronto. We partnered with OneHeart (Punjabi), Roots Community Services (Afro-Caribbean), and the Seniors Tamil Society of Peel. Participants were engaged by bilingual trainees representing each community in two workshops and one focus group thus far to explore barriers and facilitators for cardiometabolic SMES. Discussions were analyzed thematically to identify recurring themes.

**Results:** We engaged seven participants (5 women, 2 men, mean age 60.6 years [SD= 9.7]). Six participants had type 2 diabetes, 6 hypertension, 3 high cholesterol, and 1 coronary artery disease. Common barriers included traditional diets high in fat, sugar, and starch; limited time for healthy cooking and exercise; knowledge gaps and information overload at diagnosis; resistance to change among older adults; and misinformation influenced by social media. Facilitators included culturally relevant education with adaptation of traditional foods, trusted community programs and peer learning, home-based accessible exercise options, written resources to refer to, and active family involvement with shared responsibility. Unique barriers emerged: Punjabi participants trusted advice via relationships over credentials, Tamil participants reported limited awareness of Tamil-specific SMES programs, and Afro-Caribbean participants losing access to traditional medicine post-immigration.

**Conclusion:** Significant barriers and facilitators to cardiometabolic SMES exist within racialized communities. To improve equity in cardiometabolic outcomes among ethnoculturally diverse populations, cardiometabolic SMES interventions for these communities likely require tailored adaptation to meet unique cultural needs.

# Abstract 25

## Glucagon-Like Peptide-1 (GLP-1) Agonist Treatment Modulates Extracellular Vesicles Released from Isolated Human Islets During Amyloid Formation

**Rushie Tyagi**, Berkay Ozerklig, Ayesha Saleem, and Lucy Marzban

**Introduction/Background:** Reduced β-cell mass and function associated with islet inflammation is a key defect in Type 2 diabetes (T2D). Amyloid formation, caused by aggregation of human islet amyloid polypeptide (hIAPP), contributes to islet inflammation and β-cell failure in T2D, but the cellular mechanisms are unclear. We recently showed that hIAPP and its aggregates are elevated in small extracellular vesicles (sEVs) released from human islets during amyloid formation and likely act as mediators of amyloid-induced β-cell death. In this study, we examined if treatment with liraglutide, a glucagon-like peptide-1 (GLP-1) agonist, can modulate EV content of toxic hIAPP species.

**Methods:** Human islets (n=3 cadaveric donors) were cultured in normal glucose (5.5 mM) as control (no or minimal amyloid) or elevated glucose (11.1 mM; amyloid formation) without or with liraglutide (10 nM, 7 days). sEVs were isolated from islet culture medium, characterized by Tunable Resistive Pulse Sensing (TRPS), and their purity assessed by sEV markers. hIAPP and its aggregates were detected in purified sEVs by Western blot. Islet amyloid, IL-1β, and β-cell apoptosis were assessed by quantitative immunolabelling for insulin/thioflavin S, insulin/IL-1β, and insulin/TUNEL, respectively.

**Results:** Pre-culture human islets contained little or no detectable amyloid formation but culture in elevated glucose resulted in amyloid formation, which was associated with increased EV content of (pro)hIAPP and its aggregates, elevated islet IL-1β, and proportion of TUNEL-positive β-cells, as compared to islets cultured at normal glucose. Liraglutide-treated islets cultured at elevated glucose had lower amyloid formation, EV content of hIAPP species, and lower islet IL-1β and β-cell apoptosis than corresponding non-treated islets.

**Conclusion:** These findings suggest that liraglutide treatment reduces amyloid formation, modulates EV content of toxic hIAPP species, and improves β-cell survival in human islets. Treatment with GLP-1 agonists may provide a potential strategy to reduce EV content of toxic hIAPP species thereby reducing amyloid toxicity.

# Oral Presentations - Abstract 1

## Delivering Indigenous-Led Anti-Racism Training in Healthcare Settings

**Cheryl Dreaver and Tara Letandre**

**Introduction/Background:** Indigenous-specific racism in healthcare drives avoidable harm and perpetuates inequities for First Nations peoples in Canada. To address these inequities, the First Nations Health and Social Secretariat of Manitoba (FNHSSM) with partners including the Children's Hospital Research Institute of Manitoba, Diabetes Research Envisioned and Accomplished in Manitoba, Keewatinohk Inniniw Minoayawin, University of Manitoba, Health Sciences Centre, Diabetes Action Canada, and the Winnipeg Regional Health Authority, co-developed an Indigenous-led Anti-Racism Training for health professionals. Since 2021, the program has engaged dietetic interns, doctors, surgeons, graduate trainees, research staff, and community members.

**Methods:** The 10-week training begins and ends with in-person sessions including ceremony, sharing circles, orientation, and consent. Weeks 2–9 are delivered online in one-hour sessions with readings, video resources, and group discussion. Materials are grounded in Canadian contexts of First Nations health, colonization, food history, nutrition, and diabetes. Participants (n=88) were grouped in 8–10 and guided by 2–3 facilitators. Registration, pre-, and post-surveys (17 surveys, 10–36 questions) captured demographics, prior training, and attitudes toward racism.

**Results:** Of 74 participants completing both surveys, 85% identified as female, 28–31% as racialized (non-White), and 69–72% as white. Sixty-five percent reported no prior anti-racism training. Pre-surveys showed only 25% clearly understood Indigenous-specific racism and 7% had educated themselves on First Nations' healthcare experiences. Post-surveys showed significant improvement: 67% reported clear understanding, 85% educated themselves, and 91% were comfortable receiving feedback on racist behavior. Comfort using key terms (racism, oppression, privilege, colonization) rose from 30% to 83%.

**Conclusion:** An Indigenous-led, ceremony-grounded blended training improved participants' knowledge, comfort discussing racism, and confidence to intervene, and produced concrete action plans for practice change. Health systems should adopt and scale this approach with Indigenous governance. A randomized controlled evaluation is planned—funding pending—to establish causal effects on provider behaviour and patient experiences and to guide sustained system-level change.

# Abstract 2

## Beyond AIC: An Interpretive Descriptive Qualitative Study of Youth Experiences and Perceptions of Living With Type 2 Diabetes

**Oluwatoyosi Fagbuyi,** Allison Dart, Brandy Wicklow, K Pundyk, S Marks, Elizabeth Sellers, and Mandy Archibald

**Objective:** To generate an in-depth understanding of the perceptions and experiences of individuals with youth onset type 2 diabetes (T2D) to inform knowledge translation initiatives and clinical care.

**Design**: Interpretive descriptive qualitative study

**Methods:** Individuals were eligible to participate if they received a T2D diagnosis on or before age 18 years of age, reside in Manitoba, and were between 10-25 years of age at the time of data collection. Twenty-two individuals (13 females, 7 males, 2 prefer not to indicate gender; mean age=19.3 years) participated in 22 semi-structured interviews (mean length: 29:01 min) remotely using Zoom video conferencing software or by telephone. Data were analysed using inductive thematic analysis.

**Results**: Four themes were generated: (1) Low public knowledge, misconceptions and stigma impacts youth experiences including those of diagnosis, disclosure, treatment and supports; (2) shared familial experiences impact perception of the future; (3) mental and emotional wellness are critically important but require more attention; and (4) T2D carries unanticipated positive and negative impacts for youth.

**Conclusion**: Findings illustrate the complex interrelationships between public and personal conceptions of T2D, stigma, and T2D navigation, emphasizing the centrality of emotional and mental health to participants T2D experiences and management. This representation of experiences and perceptions of youth onset T2D offers direction for wholistic and youth-centered research and care, and highlights areas where further mental health and educational resources would be beneficial.

# Abstract 3

## Culturally Appropriate Self-Management Education and Support for Cardiometabolic Disease Prevention in Peel Region: A Community-Engaged Approach

**Amrit Thandi**, Joyeuse Senga, Tharsan Kanagalingam, Sebrin Sharif, Prathiga Suthanthirarajan, David Campbell, Kelly Smith, Lorraine Lipscombe, Raj Pannu, and Calvin Ke

**Introduction/Background:** Diabetes and other cardiometabolic diseases disproportionately affect racialized communities in Canada. Self-management education and support (SMES) programs are critical, but conventional approaches are resource-intensive and fail to address cultural needs. However, barriers and facilitators to SMES among local Punjabi, Tamil, and Afro-Caribbean communities are unclear.

**Methods:** We engaged adults ≥40 years with type 2 diabetes, coronary artery disease, stroke, chronic kidney disease, heart failure, or ≥2 cardiometabolic risk factors, identifying as Punjabi, Tamil, or Afro-Caribbean, and living in Peel Region or Toronto. We partnered with OneHeart (Punjabi), Roots Community Services (Afro-Caribbean), and the Seniors Tamil Society of Peel. Participants were engaged by bilingual trainees representing each community in two workshops and one focus group thus far to explore barriers and facilitators for cardiometabolic SMES. Discussions were analyzed thematically to identify recurring themes.

**Results:** We engaged seven participants (5 women, 2 men, mean age 60.6 years [SD= 9.7]). Six participants had type 2 diabetes, 6 hypertension, 3 high cholesterol, and 1 coronary artery disease. Common barriers included traditional diets high in fat, sugar, and starch; limited time for healthy cooking and exercise; knowledge gaps and information overload at diagnosis; resistance to change among older adults; and misinformation influenced by social media. Facilitators included culturally relevant education with adaptation of traditional foods, trusted community programs and peer learning, home-based accessible exercise options, written resources to refer to, and active family involvement with shared responsibility. Unique barriers emerged: Punjabi participants trusted advice via relationships over credentials, Tamil participants reported limited awareness of Tamil-specific SMES programs, and Afro-Caribbean participants losing access to traditional medicine post-immigration.

**Conclusion:** Significant barriers and facilitators to cardiometabolic SMES exist within racialized communities. To improve equity in cardiometabolic outcomes among ethnoculturally diverse populations, cardiometabolic SMES interventions for these communities likely require tailored adaptation to meet unique cultural needs.

# Abstract 4

## New Apelinergic Analogues Rescue Blood Flow Perfusion and Sensory Function in Diabetic Hind Limb Ischemia

**Marie-Sophie Lachance**, Pierre-Luc Boudreault, Philippe Sarret, and Pedro Geraldes

**Introduction/Background:** Diabetic peripheral artery disease (PAD) is characterized by impaired new blood vessel formation following ischemia, leading to high amputation risk. Although experimental pro-angiogenic therapies such as VEGF delivery have been explored, clinical outcomes remain limited. Our group has reported that apelin perfusion treatment could improve blood reperfusion in the ischemic muscle of diabetic mice. However, apelin's poor plasma stability limits its therapeutic utility. To address this, we have investigated the effects of plasma-stable apelinergic analogs (KT04-44 and AM03-68) on endothelial cell (EC) function and blood reperfusion in a diabetic hindlimb ischemia model.

**Methods:** Primary ECs were exposed to normal (5,6 mM) or high glucose (25 mM) concentrations for 48h and hypoxia (16h). EC signaling and function (proliferation, migration, and tube formation) were assessed following stimulation with analogs. Femoral artery ligation was performed in type 1 diabetic mice, and analogs were administered subcutaneously every other day for 4 weeks. Blood flow reperfusion was monitored weekly (laser Doppler). Motor capacity (voluntary wheel), mechanical (von Frey), and thermal (acetone drop) threshold were evaluated.

**Results:** Both apelinergic analogs stimulated EC proliferation, migration (2-fold), and tube formation (2.5-fold) when exposed to normal and high glucose levels. Nondiabetic mice displayed 75% blood flow reperfusion compared to 38% in diabetic mice. Diabetic mice treated with KT04-44 and AM03-68 had 81% and 75% recovery, respectively. Motor capacity and pain threshold both altered in diabetic, were improved in treated diabetic mice. VEGF-A, APLNR, and PDGF-B mRNA expression recovered with the analog treatment. Muscle fiber diameter and arteriole count were preserved in both treated diabetic mice compared to non-treated.

**Conclusion:** Local injection of apelinergic analogs rescues blood flow reperfusion, improves endothelial function, and preserves sensory capacity in diabetic mice. These analogues represent promising therapeutic candidates for reducing amputation risk and improving quality of life in patients with diabetic PAD.

# Abstract 5

## Natural Killer Cell Surveillance Eliminates Stressed Beta Cells in Type 1 Diabetes

**Jasmine Pipella**, Ian Heidinger, Jay Wieler, Jasmine Manji, Sam Kung, and Peter J. Thompson

**Introduction/Background:** During type 1 diabetes (T1D), some β-cells activate stressed states such as unfolded protein response (UPR) and senescence, which accelerate disease progression. In other tissues, senescent cells are removed through immune surveillance mechanisms involving natural killer (NK) cells but whether NK cells target stressed β-cells in T1D remains unknown. NK cells in human and mouse models of T1D exhibit impaired cytotoxicity, suggesting diminished immune surveillance. Notably, NK cell activation with double-stranded RNA mimic polyinosinic-polycytidylic acid (PolyI:C) prevents T1D in non-obese diabetic (NOD) mice, though the mechanism is unclear. This study investigated whether NK cells mediate β-cell surveillance and whether NK cell activation removes stressed β-cells during T1D.

**Methods:** Prediabetic female NOD/ShiLtJ mice received PolyI:C or phosphate buffered saline (PBS) twice weekly to activate NK cells. Glucose tolerance tests were used to assess β cell function while senescent β cell frequency, protein expression and disease progression were assessed using immunohistochemistry (IHC). Reverse-transcriptase quantitative polymerase chain reaction (RT-qPCR) was used to measure gene expression. NK cell activation by PolyI:C was confirmed using flow cytometry.

**Results**: PolyI:C treatment significantly increased NK cell activation ($p<0.0001$), with no effect in T cells ($p=0.15$) or non-NK/T cells ($p=0.95$), as expected. Additionally, PolyI:C treated mice showed slowed disease progression, increased insulin$^+$ area ($p<0.005$), and reduced insulitis ($p<0.0005$). Strikingly, examination of stress markers revealed that PolyI:C decreased senescent ($p<0.05$) and UPR ($p<0.005$) stressed β-cells, concomitant with an increase in β-cell proliferation ($p<0.005$). Cell surface proteomics identified upregulation of Calreticulin on senescent β-cells, potentially mediating interactions with NK cells.

**Conclusions:** Activating NK cells leads to a novel effect of limiting stressed β-cells while mitigating T1D progression. We propose that NK cells trigger immune surveillance that clears senescent and UPR-stressed β-cells in NOD mice.

# Abstract 6

## Sirtuin-3 Deficiency in the Liver is Associated with Mitochondrial Dysfunction and Hepatic Steatosis in Gestational Diabetes

**Khushali Trivedi**, Bo Xiang, Jewel Paskaruk, Ayesha Saleem and Vernon Dolinsky

**Introduction/Background:** Gestational diabetes mellitus (GDM) is the most common transient metabolic disorder during pregnancy. GDM significantly increases the post-pregnancy risk of type 2 diabetes and obesity. GDM is marked by insulin resistance and glucose intolerance, the underlying mechanisms remain poorly understood. Sirtuin-3 (SIRT3) is a mitochondrial NAD+-dependent deacetylase that regulates oxidative metabolism in the liver. We have previously observed reduced liver SIRT3 expression in GDM rodents.

**Hypothesis:** Liver-specific deficiency of SIRT3 impairs mitochondrial fatty acid oxidation, leading to hepatic steatosis and glucose intolerance during pregnancy, characteristic of GDM.

**Methods:** Liver-specific SIRT3 knockout mice (SIRT3-LKO) were generated by crossing $Sirt3^{tm1.1Auw}$mice from Jackson Labs with albumin-promoter driven cre-recombinase mice. SIRT3-LKO mice and controls were fed either a low-fat diet (10%kilocalorie fat) or high-fat-sucrose diet (45%kilocalorie fat) for 6-weeks before pregnancy and throughout the 3-week mouse pregnancy to induce GDM. Glucose tolerance tests were performed at gestational day 16 (GD16). Pregnant mice were sacrificed at GD18, and maternal livers were collected for histological visualization of steatosis and mitochondrial function was assessed using SeahorseXFe24 to measure complex I-and fatty acid–driven respiration in isolated liver mitochondria.

**Results:** Pregnant SIRT3-LKO mice exhibited glucose intolerance (1.3-fold, $p<0.01$) and serum insulin levels elevated by 1.5-fold ($p<0.01$) compared to controls. Histological analysis of the liver showed marked hepatic steatosis, with 1.8-fold elevated hepatic triglyceride levels($p<0.05$). Mitochondrial respiration was significantly impaired with 2.5-fold reduced fat oxidation ($p<0.001$) and 1.4-fold reduced complex I–linked basal respiration ($p<0.0001$) in SIRT3-LKO liver mitochondria.

**Conclusion:** SIRT3 is a key regulator of hepatic mitochondrial function and lipid metabolism during pregnancy, at a stage when maternal demands of energy production are high. Liver-specific SIRT3 deficiency disrupts fat oxidation and promotes steatosis, leading to hyperinsulinemia and glucose intolerance—metabolic hallmarks of GDM. Future work will assess whether activation of SIRT3 reverses hyperglycemia and hepatic steatosis during pregnancy.