



*Alberta Diabetes*  
**INSTITUTE**

# 2022 RESEARCH DAY

0815-1600 | 1-040 LKS (Oborowsky Degner Seminar Hall) & LKS Foyer

## FRIDAY OCTOBER 28

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**KEYNOTE SPEAKER**

**Peter J. Thompson, PhD**

Assistant Professor, Department of Physiology & Pathophysiology,  
University of Manitoba, Winnipeg

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**UNIVERSITY  
OF ALBERTA**

## 2022 ADI RESEARCH DAY

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### Note from the Director

Welcome to the 2022 Alberta Diabetes Institute Research Day. This annual event, hosted by ADI since 2005, provides ADI Trainees – from first year undergraduate summer students to seasoned postdoctoral fellows – the opportunity to showcase their research efforts. This year, for the first time since 2019, we are excited to host our event in-person! With the help of our dedicated ADI Trainee Working Group, ADI Members, Trainees, and Administration we have organized an exciting day of oral and poster presentations that will provide an enriching experience for everyone attending.

We are delighted to host keynote speaker Dr. Peter J. Thompson, Assistant Professor of Physiology & Pathophysiology, University of Manitoba, Winnipeg. He will be speaking on “*Beta cell stress responses in Type 1 Diabetes: emerging lessons and therapeutic opportunities.*” We are honoured that Dr. Thompson accepted our ADI Trainee Working Group members' invitation and we look forward to welcoming him back to Alberta, where he grew up, and to the ADI.

Our Research Day is intended to provide a forum to showcase the research efforts of our **ADI Trainees**. With respect to this, there are two **oral presentation** sessions (junior/senior trainees) and two **poster presentation** sessions (junior/senior trainees). During Research Day our trainees have the opportunity for direct interaction with Dr. Thompson over lunch.

The ongoing support and contributions from the Faculty of Medicine and Dentistry, the Alberta Diabetes Foundation, DRIFCan, endowments supporting the Muttart Diabetes Research & Training Centre and generous donors and other partners is deeply appreciated for their vital and sustained contributions to the work of the ADI.

I am indebted to our ADI Trainee Working Group (supported by Colleen Ruptash) for their help in organizing and running this year's ADI Research Day. I would also like to thank all our volunteers, judges, session chairs, A/V and zoom support.

We hope today will provide an opportunity to interact with and learn from your peers by listening and asking questions, further inspire your curiosity and encourage us all to pursue excellence in our scientific endeavors.

Best Regards,



Dr. Peter Senior  
Director, Alberta Diabetes Institute  
Dr. Charles A. Allard Chair in Diabetes Research  
Professor of Medicine, Division of Endocrinology and Metabolism

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### Keynote Speaker

## Peter J. Thompson, PhD



ADI is excited to announce this year's keynote speaker is Dr. Peter J. Thompson.

Dr. Thompson is an Assistant Professor in the Department of Physiology & Pathophysiology at the University of Manitoba and a Principal Investigator in the Children's Hospital Research Institute of Manitoba. He earned his BSc in molecular genetics (2007) and MSc in molecular biology (2010) at the University of Alberta, where his thesis characterized the roles of chromatin remodelling factors in mammalian development and the germline in the lab of Dr. Heather McDermid. He completed his PhD in medical genetics (2016) at the University of British Columbia in the lab of Dr. Matthew Lorincz, where he studied epigenetic mechanisms of gene regulation in embryonic stem cells. He moved into the fields of islet biology and diabetes during his postdoctoral fellowship at the University of California San Francisco (UCSF, 2016-2020), where his work discovered senescence as a new form of beta

cell dysfunction in type 1 diabetes (T1D). He was funded by the Diabetes Research Connection, the Larry L. Hillblom Foundation and the Program for Breakthrough Biomedical Research at UCSF. He started his independent position at the University of Manitoba and Children's Hospital Research Institute of Manitoba in 2020, where his research program explores beta cell stress responses and their crosstalk with the immune system in the pathogenesis of T1D with the goal of developing new therapies.

On October 28, from 0845-0945, Dr. Thompson will be talking about "***Beta cell stress responses in Type 1 Diabetes: emerging lessons and therapeutic opportunities***". We would also like to thank Dr. Thompson for serving on the trainee oral presentation judge panel.

Welcome Dr. Thompson!

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### Morning & Afternoon Schedule

## MORNING SESSION

### WELCOME

0815-0834	Welcome to 2022 Research Day	Refreshments in the LKS Foyer
0835-0839	Opening Remarks	Dr. Peter Senior, ADI Director
0840-0844	Introduction to Keynote Speaker	Theodore Dos Santos, ADI Trainee Working Group Chair

### KEYNOTE SPEAKER

0845-0945	Dr. Peter J. Thompson Assistant Professor, Department of Physiology & Pathophysiology, University of Manitoba	BETA CELL STRESS RESPONSES IN TYPE 1 DIABETES: EMERGING LESSONS AND THERAPEUTIC OPPORTUNITIES
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### POSTER PRESENTATION - SENIOR

0946-1044	Theodore dos Santos MacDonald Lab	PhD student	<b>Page 1</b>	INVESTIGATING ALPHA AND BETA CELL PHENOTYPES IN TYPE 1 DIABETES
	Kholoud Elmihi Jacobs Lab	PhD student	<b>Page 2</b>	THE REGULATORY EFFECT OF ETNPPL ON CHOLESTEROL BIOSYNTHESIS PATHWAY IN MICE
	Olawale Johnson Ogunsile Pepper Lab	PhD student	<b>Page 3</b>	QUANTITATIVE AND PHENOTYPIC CHARACTERIZATION OF CD8+T CELLS IN THE CONTEXT OF PANCREAS TRANSPLANTATION
	Amanda Schukarucha Gomes MacDonald Lab	PhD student	<b>Page 4</b>	GLYCINE RECEPTOR ACTIVITY IN $\beta$ CELLS IS DOWNREGULATED IN TYPE 2 DIABETES AND AFTER HIGH GLUCOSE CULTURE
	Kevin Verhoeff Shapiro Lab	PhD student	<b>Page 5</b>	EVALUATING THE POTENTIAL FOR ABO-INCOMPATIBLE ISLET TRANSPLANTATION: EXPRESSION OF ABH ANTIGENS ON HUMAN PANCREATA, ISOLATED ISLETS, AND EMBRYONIC STEM CELL-DERIVED ISLETS
	Emad Yuzbashian Chan Lab	PhD student	<b>Page 6</b>	DAIRY PRODUCT CONSUMPTION AND RISK OF NON-ALCOHOLIC FATTY LIVER DISEASE: A SYSTEMATIC REVIEW AND META-ANALYSIS OF EVIDENCE FROM OBSERVATIONAL STUDIES
	Nerea Cuesta Gomez Shapiro Lab	Postdoctoral Fellow	<b>Page 7</b>	THREE-DIMENSIONAL CULTURE ENHANCES IN VIVO AND IN VITRO QUALITY OF INDUCED PLURIPOTENT STEM CELLS
	Qutuba Karwi Lopaschuk Lab	Postdoctoral Fellow	<b>Page 8</b>	THE ROLE OF ALTERED BRANCHED-CHAIN AMINO ACID OXIDATION IN MEDIATING CARDIAC INSULIN RESISTANCE IN HEART FAILURE

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### Morning & Afternoon Schedule

#### ORAL PRESENTATION - JUNIOR

**SESSION CHAIR: Dr. Jessica Yue**

1045-1055	Hailey Fedoruk Jacobs Lab	MSc student	<b>Page 9</b>	DIETARY TRIMETHYLAMINE N-OXIDE (TMAO) SUPPLEMENTATIONS ATTENUATES WEIGHT GAIN AND HEPATIC GLUCOSE METABOLISM IN MICE FED A HIGH-FAT DIET
1057-1107	Mantash Grewal Yue Lab	MSc student	<b>Page 10</b>	HYPOTHALAMIC GLUCAGON INFUSION REGULATES HEPATIC TRIGLYCERIDE SECRETION
1109-1119	Nandini Basuray Haqq Lab	MSc student	<b>Page 11</b>	FIBER SUPPLEMENTATION AND METFORMIN COMBINATION THERAPY IN ADOLESCENTS WITH SEVERE OBESITY AND INSULIN RESISTANCE: INTERACTIONS WITH THE GUT MICROBIOME: PROGRESS AND CHALLENGES
1121-1131	Jordan Wong Pepper Lab	MSc/MD student	<b>Page 12</b>	EXPLORING LOCAL IMMUNE MODULATION WITH RAPAMYCIN-ELUTING MICELLES TO PRESERVE ISLET GRAFT FUNCTION IN MICE
1133-1143	Megan Macasaet Richard Lab	Undergrad student	<b>Page 13</b>	IMMUNOPHENOTYPIC CHARACTERIZATION OF DENDRITIC CELLS IN INDIVIDUALS WITH OBESITY AND VARYING LEVELS OF GLYCEMIA
1145-1155	Corbin Nitz Yardley Lab	Undergrad student	<b>Page 14</b>	BLOOD GLUCOSE RESPONSE TO MORNING FASTED RESISTANCE EXERCISE IS MORE CONSISTENT THAN POSTPRANDIAL EXERCISE IN ADULTS WITH TYPE 1 DIABETES

### TRAINEE LUNCH WITH THE SPEAKER

1210-1330	Lister Centre, Glacier Room (about a 10 minute walk from the LKS)  <b>By invitation:</b> ADI Trainee Research Day Presenters / ADI Research Day Trainee Volunteers	<b>Guest Dr. Peter J. Thompson / Hosts ADI Trainees</b> LUNCH PROVIDED
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### AFTERNOON SESSION

#### POSTER PRESENTATION - JUNIOR

1345-1444	Roozbeh Akbari Motlagh Buteau Lab	MSc student	<b>Page 15</b>	A SMALL MOLECULE ACTIVATOR OF LYN IMPROVES THE OUTCOMES OF ISLET TRANSPLANTATION IN MICE
	Zhiqian (Rita) Jiang Mager Lab	MSc student	<b>Page 16</b>	DETERMINATION OF FRAILTY STATUS USING DIFFERENT TOOLS IN THE COMMUNITY-DWELLING ADULTS WITH DIABETES MELLITUS AND CHRONIC KIDNEY DISEASE
	Qiuyu Sun Lopaschuk Lab	MSc student	<b>Page 17</b>	CARDIAC GLUCOSE OXIDATION IS IMPAIRED IN HEART FAILURE WITH PRESERVED EJECTION FRACTION (HFpEF)

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### Morning & Afternoon Schedule

#### POSTER PRESENTATION - JUNIOR

	Boyan Vasilev Yue Lab	MSc student	<b>Page 18</b>	GLUCOCORTICOID ACTION IN THE NUCLEUS OF THE SOLITARY TRACT AFFECTS HEPATIC VLDL-TG SECRETION
	Xiaoying Wu Vine Lab	MSc student	<b>Page 19</b>	PRE-DIABETES AND EARLY ATHEROSCLEROTIC CARDIOVASCULAR DISEASE IN YOUNG WOMEN WITH AND WITHOUT POLYCYSTIC OVARY SYNDROME
	Adnan Black Rayat Lab	Undergrad student	<b>Page 20</b>	EXPRESSION OF VASCULAR ENDOTHELIAL CADHERIN AND ENDOTHELIAL CELLS IN DEVELOPING PORCINE ISLETS
	Tate Erickson West Lab	Undergrad student	<b>Page 21</b>	ENZYMATIC REMOVAL OF ABO-A-ANTIGEN IN A MOUSE MODEL OF ABO-INCOMPATIBLE TRANSPLANTATION ( <i>Bruce Motyka presenting</i> )
	Dineli Fernando Chan Lab	Undergrad student	<b>Page 22</b>	THE EFFECT OF DAIRY PRODUCTS ON LIVER LIPID ACCUMULATION IN A MOUSE MODEL OF PRE-DIABETES
	Alexandra Knox Chan Lab	Undergrad student	<b>Page 23</b>	THE EFFECT OF IRW (ILE-ARG-TRP) ON LIVER LIPID ACCUMULATION IN OBESE AND INSULIN RESISTANT C56BL/6 MICE.
	Kevin Zhan Anderson Lab	Undergrad student	<b>Page 24</b>	LOCALIZED IMMUNE CELL DEPLETION TREATMENT IN THE PANCREAS OF NEW ONSET NOD DIABETIC MICE

#### ORAL PRESENTATION - SENIOR

#### SESSION CHAIR: Dr. Jane Yardley

1445-1455	Jasmine Maghera MacDonald Lab	PhD student	<b>Page 25</b>	ELECTROPHYSIOLOGICAL CHARACTERIZATION OF STEM-CELL DERIVED $\beta$ -CELLS TO HELP PRODUCE CLINICALLY RELEVANT CELLS FOR TRANSPLANT
1457-1507	Michaelann Wilke Vine Lab	Research associate	<b>Page 26</b>	AWARENESS AND FOLLOW UP HEALTH CARE IS LIMITED FOR WOMEN WITH POLYCYSTIC OVARIAN SYNDROME AT HIGH-RISK FOR DIABETES AND HEART DISEASE
1509-1519	Janyne Johnson Light Lab	PhD student	<b>Page 27</b>	THE EMERGING ROLE OF ALPHA-CELL GLUCAGON-LIKE PEPTIDE-1 (GLP-1)
1521-1531	ILA Tewari Jasra Shapiro Lab	Postdoctoral fellow	<b>Page 28</b>	GENERATION AND CHEMICAL ABLATION OF OFF-TARGETS CELLS FROM AUTOLOGOUS STEM CELLS DERIVED ISLETS CELL PRODUCTS TO TREAT DIABETES
1533-1543	Hui Huang Buteau Lab	Postdoctoral fellow	<b>Page 29</b>	A NOVEL SMALL-MOLECULE ACTIVATOR OF LYN KINASE FOR THE TREATMENT OF TYPE 1 DIABETES
1545-1555	Kim Ho Lopaschuk Lab / Ussher Lab	PhD student	<b>Page 30</b>	THE KETOGENIC DIET BLUNTS INSULIN-STIMULATED GLUCOSE OXIDATION IN THE FAILING HEART

#### CLOSING REMARKS

1556-1600	Closing Remarks	Dr. Peter Senior, ADI Director
	Awards announced Monday, October 31	

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### Awards

Prize winners will be notified by email on October 31 and announced via ADI Update and social media.

#### ORAL PRESENTATION SESSION (Junior Trainees)

- 1 Best Award & 1 Honourable Mention

#### ORAL PRESENTATION SESSION (Senior Trainees)

- 1 Best Award & 1 Honourable Mention

#### POSTER SESSION (Junior Trainees)

- 1 Best Award & 1 Honourable Mention

#### POSTER SESSION (Senior Trainees)

- 1 Best Award & 1 Honourable Mention



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<b>BASURAY</b> Nandini (Haqq Lab)	<b>11</b>	FIBER SUPPLEMENTATION AND METFORMIN COMBINATION THERAPY IN ADOLESCENTS WITH SEVERE OBESITY AND INSULIN RESISTANCE: INTERACTIONS WITH THE GUT MICROBIOME: PROGRESS AND CHALLENGES
<b>BLACK</b> Adnan (Rayat Lab)	<b>20</b>	EXPRESSION OF VASCULAR ENDOTHELIAL CADHERIN AND ENDOTHELIAL CELLS IN DEVELOPING PORCINE ISLETS
<b>CUESTA GOMEZ</b> Nerea (Shapiro Lab)	<b>7</b>	THREE-DIMENSIONAL CULTURE ENHANCES IN VIVO AND IN VITRO QUALITY OF INDUCED PLURIPOTENT STEM CELLS
<b>DOS SANTOS</b> Theodore (MacDonald Lab)	<b>1</b>	INVESTIGATING ALPHA AND BETA CELL PHENOTYPES IN TYPE 1 DIABETES
<b>ELMIHI</b> Kholoud (Jacobs Lab)	<b>2</b>	THE REGULATORY EFFECT OF ETNPPL ON CHOLESTEROL BIOSYNTHESIS PATHWAY IN MICE
<b>ERICKSON</b> Tate (West Lab)	<b>21</b>	ENZYMATIC REMOVAL OF ABO-A-ANTIGEN IN A MOUSE MODEL OF ABO-INCOMPATIBLE TRANSPLANTATION ( <i>Bruce Motyka presenting</i> )
<b>FEDORUK</b> Hailey (Jacobs Lab)	<b>9</b>	DIETARY TRIMETHYLAMINE N-OXIDE (TMAO) SUPPLEMENTATIONS ATTENUATES WEIGHT GAIN AND HEPATIC GLUCOSE METABOLISM IN MICE FED A HIGH-FAT DIET
<b>FERNANDO</b> Dineli (Chan Lab)	<b>22</b>	THE EFFECT OF DAIRY PRODUCTS ON LIVER LIPID ACCUMULATION IN A MOUSE MODEL OF PRE-DIABETES
<b>GREWAL</b> Mantash (Yue Lab)	<b>10</b>	HYPOTHALAMIC GLUCAGON INFUSION REGULATES HEPATIC TRIGLYCERIDE SECRETION
<b>HO</b> Kim (Lopaschuk Lab) / (Ussher Lab)	<b>30</b>	THE KETOGENIC DIET BLUNTS INSULIN-STIMULATED GLUCOSE OXIDATION IN THE FAILING HEART
<b>HUANG</b> Hui (Buteau Lab)	<b>29</b>	A NOVEL SMALL-MOLECULE ACTIVATOR OF LYN KINASE FOR THE TREATMENT OF TYPE 1 DIABETES
<b>JIANG</b> Zhiqian (Rita) (Mager Lab)	<b>16</b>	DETERMINATION OF FRAILTY STATUS USING DIFFERENT TOOLS IN THE COMMUNITY-DWELLING ADULTS WITH DIABETES MELLITUS AND CHRONIC KIDNEY DISEASE
<b>JOHNSON</b> Janyne (Light Lab)	<b>27</b>	THE EMERGING ROLE OF ALPHA-CELL GLUCAGON-LIKE PEPTIDE-1 (GLP-1)
<b>KARWI</b> Qutuba (Lopaschuk Lab)	<b>8</b>	THE ROLE OF ALTERED BRANCHED-CHAIN AMINO ACID OXIDATION IN MEDIATING CARDIAC INSULIN RESISTANCE IN HEART FAILURE
<b>KNOX</b> Alexandra (Chan Lab)	<b>23</b>	THE EFFECT OF IRW (ILE-ARG-TRP) ON LIVER LIPID ACCUMULATION IN OBESE AND INSULIN RESISTANT C56BL/6 MICE.

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<b>MAGHERA</b> Jasmine (MacDonald Lab)	<b>25</b>	ELECTROPHYSIOLOGICAL CHARACTERIZATION OF STEM-CELL DERIVED $\beta$ -CELLS TO HELP PRODUCE CLINICALLY RELEVANT CELLS FOR TRANSPLANT
<b>NITZ</b> Corbin (Yardley Lab)	<b>14</b>	BLOOD GLUCOSE RESPONSE TO MORNING FASTED RESISTANCE EXERCISE IS MORE CONSISTENT THAN POSTPRANDIAL EXERCISE IN ADULTS WITH TYPE 1 DIABETES
<b>OGUNSILE</b> Olawale Johnson (Pepper Lab)	<b>3</b>	QUANTITATIVE AND PHENOTYPIC CHARACTERIZATION OF CD8+T CELLS IN THE CONTEXT OF PANCREAS TRANSPLANTATION
<b>SCHUKARUCHA GOMES</b> Amanda (MacDonald Lab)	<b>4</b>	GLYCINE RECEPTOR ACTIVITY IN $\beta$ CELLS IS DOWNREGULATED IN TYPE 2 DIABETES AND AFTER HIGH GLUCOSE CULTURE
<b>SUN</b> Qiuyu (Lopaschuk Lab)	<b>17</b>	CARDIAC GLUCOSE OXIDATION IS IMPAIRED IN HEART FAILURE WITH PRESERVED EJECTION FRACTION (HFpEF)
<b>TEWARI JASRA</b> ILA (Shapiro Lab)	<b>28</b>	GENERATION AND CHEMICAL ABLATION OF OFF-TARGETS CELLS FROM AUTOLOGOUS STEM CELLS DERIVED ISLETS CELL PRODUCTS TO TREAT DIABETES
<b>VASILEV</b> Boyan (Yue Lab)	<b>18</b>	GLUCOCORTICOID ACTION IN THE NUCLEUS OF THE SOLITARY TRACT AFFECTS HEPATIC VLDL-TG SECRETION
<b>VERHOEFF</b> Kevin (Shapiro Lab)	<b>5</b>	EVALUATING THE POTENTIAL FOR ABO-INCOMPATIBLE ISLET TRANSPLANTATION: EXPRESSION OF ABH ANTIGENS ON HUMAN PANCREATA, ISOLATED ISLETS, AND EMBRYONIC STEM CELL-DERIVED ISLETS
<b>WILKE</b> Michaelann (Vine Lab)	<b>26</b>	AWARENESS AND FOLLOW UP HEALTH CARE IS LIMITED FOR WOMEN WITH POLYCYSTIC OVARIAN SYNDROME AT HIGH-RISK FOR DIABETES AND HEART DISEASE
<b>WONG</b> Jordan (Pepper Lab)	<b>12</b>	EXPLORING LOCAL IMMUNE MODULATION WITH RAPAMYCIN-ELUTING MICELLES TO PRESERVE ISLET GRAFT FUNCTION IN MICE
<b>WU</b> Xiaoying (Vine Lab)	<b>19</b>	PRE-DIABETES AND EARLY ATHEROSCLEROTIC CARDIOVASCULAR DISEASE IN YOUNG WOMEN WITH AND WITHOUT POLYCYSTIC OVARY SYNDROME
<b>YUZHASHIAN</b> Emad (Chan Lab)	<b>6</b>	DAIRY PRODUCT CONSUMPTION AND RISK OF NON-ALCOHOLIC FATTY LIVER DISEASE: A SYSTEMATIC REVIEW AND META-ANALYSIS OF EVIDENCE FROM OBSERVATIONAL STUDIES
<b>ZHAN</b> Kevin (Anderson Lab)	<b>24</b>	LOCALIZED IMMUNE CELL DEPLETION TREATMENT IN THE PANCREAS OF NEW ONSET NOD DIABETIC MICE

# **ABSTRACTS**

Morning Session

## **Poster Presentation**

### **SENIOR**

Pages 1-8



# Abstracts

## **INVESTIGATING ALPHA AND BETA CELL PHENOTYPES IN TYPE 1 DIABETES**

Theodore dos Santos, XiaoQing Dai, Cara Ellis, Robert C. Jones, Joan Camunas-Soler, Austin Bautista, Patrick E. MacDonald

Department of Pharmacology, Faculty of Medicine and Dentistry, Alberta Diabetes Institute, University of Alberta

**Background:** In type 1 diabetes (T1D),  $\beta$ -cells are destroyed by autoimmunity, resulting in lifelong dependencies on insulin therapy. There is considerable heterogeneity in the pathology, genetics, and response to therapies in T1D [1]; however, little research has focused on how the  $\alpha$ -cells and surviving  $\beta$ -cells behave. Our previous work studying type 2 diabetes (T2D) showed that  $\alpha$ -cell impairment is heterogeneous and contributes to poor blood glucose control. Here, we apply a similar rationale to investigate the behaviours of endocrine cells in T1D. Further, as there is considerable native heterogeneity in  $\alpha$ - and  $\beta$ -cell behaviour, we predict that  $\alpha$ - and  $\beta$ -cell dysfunction in T1D is likely heterogeneous.

**Methods:** We used combined patch-clamp electrophysiology and scRNAseq (Patch-Seq) to record electrical behaviour and transcript expression in  $\alpha$ - and  $\beta$ -cells from human donor islets. Uniform Manifold Approximation and Projection (UMAP) approaches were employed to analyze the transcriptome of T1D islet cells from matched (age, sex, and BMI) non-diabetes (ND) donors. Previously developed machine-learning methods were applied to score electrophysiologic phenotypes of  $\alpha$ - and  $\beta$ -cells in T1D and ND. Differential gene expression analysis combined with gene set enrichment tools were employed to identify pathways that were differentially regulated in ND vs T1D  $\alpha$ - and  $\beta$ -cells.

**Results:** Compared to controls, T1D  $\alpha$ -cells demonstrate significantly altered electrophysiology with increased exocytosis and ion currents, whilst  $\beta$ -cells were comparable. However, modelling revealed a significant decrease in both  $\alpha$ - and  $\beta$ -cell scores in T1D, suggesting that when analysed holistically, overall electrical identity is altered. UMAP analysis of gene expression revealed  $\alpha$ -cell subtypes that were enriched in T1D. Last, pathways involved in the neurohormonal, and metabolic amplifications pathways were enriched in  $\alpha$ -cells of T1D donors, while pathways involved in auto-immunity disease were upregulated in T1D  $\beta$ -cells.

**Conclusions:** In T1D,  $\alpha$ -cells demonstrate altered electrical identity and gene expression profiles. On the other hand,  $\beta$ -cells transcriptomes in T1D are comparable to ND, as are their electrical properties when analyzed independently. However, when modelled holistically, T1D  $\beta$ -cells possess significantly altered electrical identities compared to ND, requiring further investigation. Next, we will identify genes and pathways linked to the altered behaviour we observe in T1D.

**Keywords:** Type 1 Diabetes, Electrophysiology, Single Cell RNA Sequencing, Machine Learning, Gene Set Enrichment Analysis

# Abstracts

## THE REGULATORY EFFECT OF *ETNPPL* ON CHOLESTEROL BIOSYNTHESIS PATHWAY IN MICE

**Kholoud Elmihi**, Kelly-Ann Leonard, Randy Nelson, Aducio Thiesen, Robin D. Clugston, René L. Jacobs.

Department of Agricultural, Food & Nutritional Science, Faculty of Agricultural, Life & Environmental Sciences.

### Background and Hypothesis

Ethanolamine phosphate phospholyase (ETNPPL) is an enzyme that degrades phospho-ethanolamine to acetaldehyde, ammonia, and hydrogen phosphate. ETNPPL is primarily expressed in the liver and the brain. We have found that ETNPPL is expressed in the nucleus, where it could serve a dual role. First, ETNPPL may remove substrates for phosphatidylethanolamine synthesis, thus regulating cellular phospholipid balance. Second, ETNPPL may provide substrates for acetyl CoA production in the nucleus, thereby affecting the acetylation of nuclear receptors and proteins.

### Methods

*Etnppl*<sup>-/-</sup> and *Etnppl*<sup>+/+</sup> mice were developed in our lab from heterozygous parents (*Etnppl*<sup>+/-</sup>; purchased from Taconic Biosciences). Mice were fed either a chow diet (CD) or a high-fat diet (HFD) (45% kcal fat for ten weeks) and samples were collected following an overnight fast. Plasma and hepatic tissues were analyzed HPLC. RNA was extracted from hepatic tissues using TRIZOL to be used for RNA sequencing analysis. Additionally, hepatic tissues were examined by hematoxylin and eosin staining.

### Results

Independent of diet, *Etnppl*<sup>-/-</sup> mice have higher plasma triglycerides and apolipoprotein B100 than *Etnppl*<sup>+/+</sup> mice, indicating increased VLDL particles in the plasma. CD-fed *Etnppl*<sup>-/-</sup> mice had increased plasma cholesterol esters as compared to *Etnppl*<sup>+/+</sup> mice. However, when fed a HFD, both plasma and hepatic cholesterol were decreased in *Etnppl*<sup>-/-</sup> mice compared to *Etnppl*<sup>+/+</sup> mice. Hepatic phospholipids were not significantly different between genotypes in the two feeding trials. Hepatic tissues showed lower steatosis in *Etnppl*<sup>-/-</sup> mice than in *Etnppl*<sup>+/+</sup> mice fed a HFD, although hepatic TG levels were unaltered. Interestingly, HFD-fed *Etnppl*<sup>-/-</sup> mice were resistant to diet-induced obesity and exhibited higher energy expenditure than *Etnppl*<sup>+/+</sup> mice. RNA sequencing data showed alterations in cholesterol metabolism with both dietary conditions.

### Conclusion

We have discovered that ETNPPL is a novel regulator of hepatic cholesterol homeostasis. Studies are ongoing to investigate the potential mechanism(s).

**Keywords:** Cholesterol, VLDL, acetyl CoA, nucleus.

# Abstracts

## QUANTITATIVE AND PHENOTYPIC CHARACTERIZATION OF CD8+ T CELLS IN THE CONTEXT OF PANCREAS TRANSPLANTATION

Olawale Johnson Ogunsile<sup>1,2,3</sup>, Paola Stephanie Apaolaza<sup>1</sup>, Andrew Pepper<sup>3</sup>, Teresa Rodriguez-Calvo<sup>1</sup>

<sup>1</sup> Institute of Diabetes Research, Helmholtz Center Munich, Germany, <sup>2</sup> Ludwig Maximilians University, Munich, Germany, <sup>3</sup> Department of Surgery, Alberta Diabetes Institute, University of Alberta, Edmonton, Canada.

**Background:** Despite marked progress in clinical islet and pancreas transplantation, several obstacles remain precluding its widespread use. While auto- and allo-immune mediated rejection clearly contribute to long-term graft failure, mounting evidence suggests that T cell infiltration, induced by inflammatory responses in the peri-transplant period, severely compromises engraftment. Although both CD4+ and CD8+ T cells contribute to the rejection process, with the latter playing a major role, there is still a clear knowledge gap regarding the phenotype, function, and specificity of CD8+ T cells infiltrating the pancreas and pancreatic islet grafts in the context of transplantation. This underlines the significance of further quantitative and phenotypic analysis, of not only autoreactive but of all the CD8+ T cells present in the pancreas and within islet grafts post-transplant. Our objective is to understand the pathogenic role of CD8+ T cells in graft rejection and/or possible recurrent autoimmunity.

**Methods:** Human peripheral blood mononuclear cells (PBMCs) and isolated CD8s were used for the technical optimization of the immunostaining panel for identifying CD8+ T cells in our tissues of interest. Frozen human tissue sections were obtained from the Network for Pancreatic Organ donors with Diabetes (nPOD). Pre- and post-transplantation pancreas sections, along with pancreatic lymph nodes (pLNs), and spleen were immunostained after proper antibody validation. The quantification of the CD8+ T cell population in whole slide-scanned images of tissues was performed with QuPath, an open-source digital pathology analysis software.

**Summary of Results:** We developed, optimized, and validated staining panels for characterizing CD8+ T cells in our tissue samples. Our results showed a higher proportion and density of CD8+ T cells in the transplant pancreas when compared to the native pancreas from T1D individuals, while the non-diabetes control group has less frequency when compared to these two groups. Also, there is an enrichment of CD8+ T cells in the spleen of T1D donors, which almost tripled the proportion of CD8+ T cells in the spleen of the donors without diabetes.

**Conclusions:** An increased density and frequency of CD8+ T cells in transplant pancreas could suggest an active autoimmune response against the beta cells, or a prominent role in pancreas graft rejection. More so, a significantly high proportion of CD8+ T cells in the spleen of T1D patients could connote migration to other tissues like the pLNs where activation and initial priming of autoreactive T cells occur. These CD8+ T cells could then recirculate or migrate to inflamed pancreas. Consequently, this may indicate a possible indirect role of the spleen of T1D subjects, not only in the activation or reactivation of autoimmunity but also in graft rejection.

**Keywords:** Pancreas transplantation, autoimmunity, infiltrating CD8+ T cells, graft rejection

# Abstracts

## GLYCINE RECEPTOR ACTIVITY IN $\beta$ CELLS IS DOWNREGULATED IN TYPE 2 DIABETES AND AFTER HIGH GLUCOSE CULTURE

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**Background:** Glycine receptors (GlyRs) are present in human  $\beta$  cells, and mediate glycine-evoked currents that contribute to cell depolarization, increasing insulin secretion. However, in islets from type 2 diabetic donors, GlyR activity is impaired, and the mechanisms that lead to this change are still unknown. We aimed to further investigate how the GlyRs can influence islet function, and if the GlyR dysfunction in type 2 diabetes (T2D) is caused by hyperglycemia.

**Methods:** Human islets from donors with and without T2D were dispersed into single cells and cultured in 5.5 mM or 15 mM glucose for 2 days. Glycine currents were measured through the whole-cell patch-clamp technique, at the holding membrane potential of -70 mV, in the presence and absence of 300  $\mu$ M glycine and 10  $\mu$ M strychnine (a GlyR antagonist). The identity of the cells was later confirmed by insulin immunostaining. The expression of the GlyR  $\alpha$ 1,  $\alpha$ 3 and  $\beta$  mRNA splice variants was quantified and compared between islets from non-diabetic and T2D donors.

**Results:** The glycine-evoked currents in  $\beta$  cells from donors with T2D ( $-0.7690$  pA/pF  $\pm$   $0.5298$ ,  $n=7$ ) were smaller than those measured in cells from donors without diabetes ( $-9.679$  pA/pF  $\pm$   $2.068$ ,  $n=29$ ). The  $\beta$  cells cultured in 15 mmol/L glucose for 2 days had smaller glycine-evoked currents ( $-6.121$  pA/pF  $\pm$   $2.055$ ,  $n=10$ ) than those in control media ( $-13.16$  pA/pF  $\pm$   $3.746$ ,  $n=11$ ). However, the expression of most GlyR subunit mRNA splice variants was overall decreased in islets of donors with T2D, with no evidence of a shift in alternative splicing.

**Conclusions:** Glycine-evoked currents in  $\beta$  cells are decreased after 2 days of culture with high glucose, showing that hyperglycemia is capable of modulating GlyRs. This is similar to the reduced glycine-evoked current in T2D, where we find a decrease in overall GlyR gene expression, but not a shift in GlyR mRNA splicing.

**Keywords:** Islets,  $\beta$ -cells, Glycine, Neurotransmitters, Hyperglycemia



# Abstracts

## **EVALUATING THE POTENTIAL FOR ABO-INCOMPATIBLE ISLET TRANSPLANTATION: EXPRESSION OF ABH ANTIGENS ON HUMAN PANCREATA, ISOLATED ISLETS, AND EMBRYONIC STEM CELL-DERIVED ISLETS**

Kevin Verhoeff, Nerea Cuesta-Gomez, Patrick Albers, Rena Pawlick, Braulio A. Marfil-Garza, Ila Jasra, Nidheesh Dadheech, Doug O’Gorman, Tatsuya Kin, Anne Halpin, Lori J. West, A.M. James Shapiro

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**Background:** ABO-incompatible transplantation has improved accessibility of kidney, heart, and liver transplantation. Pancreatic islet transplantation continues to be ABO-matched, yet ABH antigen expression within isolated human islets, or novel human embryonic stem cell (hESC)-derived islets remains uncharacterized.

**Methods:** We evaluated ABH glycans within human pancreata, isolated islets, hESC-derived pancreatic progenitors, and the ensuing *in vivo* mature islets following kidney subcapsular transplantation in rats. Analyses include fluorescence immunohistochemistry and single-cell analysis using flow cytometry.

**Results:** Within the pancreas, endocrine and ductal cells do not express ABH antigens. Conversely, pancreatic acinar tissues strongly express these antigens. Acinar tissues are present in a substantial portion of cells within islet preparations obtained for clinical transplantation. hESC-derived pancreatic progenitors and their ensuing *in vivo*-matured islet-like clusters do not express ABH antigens.

**Conclusions:** Clinical pancreatic islet transplantation should remain ABO-matched due to contaminant acinar tissue within islet preparations that express ABH glycans. Alternatively, hESC-derived pancreatic progenitors and the resulting *in vivo*-matured hESC-derived islets do not express ABH antigens. These findings introduce the potential for ABO-incompatible cell replacement treatment and offers evidence to support scalability of hESC-derived cell therapies in type 1 diabetes.

**Keywords:** islet transplantation; embryonic stem cell-derived islet transplantation; transplant; ABO-compatibility; ABH glycans



# Abstracts

## **DAIRY PRODUCT CONSUMPTION AND RISK OF NON-ALCOHOLIC FATTY LIVER DISEASE: A SYSTEMATIC REVIEW AND META-ANALYSIS OF EVIDENCE FROM OBSERVATIONAL STUDIES**

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**Background and aim:** Insulin resistance, obesity and metabolic syndrome are all linked to non-alcoholic fatty liver disease (NAFLD), making it the most frequent form of chronic liver disease. Although dairy products are a component of healthy eating patterns, their association with the risk of NAFLD is debated. Thus, we aimed to establish a comprehensive and quantifiable association of total dairy and specific dairy product consumption with the risk of NAFLD by conducting a systematic review and meta-analysis of observational studies.

**Methods:** We searched PubMed, Web of Science and Scopus databases to identify observational studies on the association of dairy consumption with NAFLD risk published before March 1, 2022. A random-effects model was used to compute the summary risk estimates. For the meta-analysis, reported odds ratios (ORs) of fully adjusted models and their confidence intervals (CIs) were extracted. Heterogeneity between studies was assessed using Cochran's Q- and I<sup>2</sup> tests. Out of 6470 documents, 11 epidemiological/observational studies, including 43,649 participants and 11,020 cases, were entered into our systematic review and meta-analysis.

**Results:** The pooled OR from the random-effects model indicated a significant association between dairy consumption and risk of NAFLD (OR=0.90; 95% CI: 0.83, 0.98) with substantial heterogeneity among the studies (I<sup>2</sup> = 67.8%, P-heterogeneity < 0.001). Despite moderate to considerable heterogeneity, these associations remained consistent across multiple subgroups. The reduced risk of NAFLD was marginally significant when comparing the highest versus lowest total dairy consumption categories (RR: 0.92; 95% CI: 0.83, 1.01). Pooling ORs revealed that milk consumption was inversely associated with NAFLD risk (OR: 0.86; 95% CI: 0.78, 0.95). Even though higher consumption of yogurt and high-fat dairy was linked to a lower risk of NAFLD, eating more cheese was not linked to the risk of NAFLD.

**Conclusion:** Our results imply that higher dairy consumption, especially milk and yogurt, was associated with a lower NAFLD risk. Further well-designed studies are vital to clarify this association and shed light on the underlying mechanisms.

**Keywords:** milk, yogurt, meta-analysis, non-alcoholic fatty liver disease

# Abstracts

## THREE-DIMENSIONAL CULTURE ENHANCES IN VIVO AND IN VITRO QUALITY OF INDUCED PLURIPOTENT STEM CELLS

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**Background:** Induced pluripotent stem cells (iPSCs) possess great potential to revolutionize the field of precision health and regenerative medicine. iPSCs offer a renewable source to generate islets, dopaminergic neurons, retinal cells, and cardiomyocytes for cell replacement therapies. However, mass manufacturing of iPSCs remains critical for clinical translation of regenerative cell therapies.

**Methods:** Sendai virus transfection of human peripheral blood mononuclear cells was used to establish a genomically stable, mycoplasma- and virus-free iPSC line. Herein, we comparatively evaluated expansion capacity, viability, genomic integrity, pluripotency phenotype and *in vivo* pluripotency potential of iPSCs expanded within two-dimensional (2D - planar) and three-dimensional (3D - suspension) culture conditions. Identical cell products and characteristics were used for both setups.

**Results:** 101.1-fold (SD 15.6) expansion of iPSCs in 3D culture compared to 19.1 (SD 2.5) in 2D ( $p < 0.0001$ ) was observed without significant differences in cell viability among groups. Improved expansion in 3D conditions was associated with increased proliferation, measured as Ki67<sup>+</sup> expression using flow cytometry (80% vs 60%,  $p = 0.0022$ ). Moreover, flow cytometry showed a higher frequency of pluripotency marker (Oct4<sup>+</sup>Nanog<sup>+</sup>Sox2<sup>+</sup>) expression in 3D vs 2D cells (94.3% [SD1.4] vs 52.5% [SD 5.6],  $p = 0.0079$ ). Karyotype analysis demonstrated genomic integrity in both groups, even after long-term passaging (>25). Following renal subcapsular transplant, both 2D- and 3D-cultured iPSCs produced mature teratomas. 2D-expanded cells generated predominantly solid teratomas, while 3D-expanded cells produced more mature and predominantly cystic teratomas. Lower percentages of proliferative cells (Ki67<sup>+</sup>) were observed in teratomas generated from 3D-expanded cells compared to 2D (18.3% [SD 2.2] vs 45.3% [SD 2.1],  $p=0.0022$ ).

**Conclusion:** In conclusion, compared to adherent 2D culture, 3D suspension cultures allow increased expansion of iPSC with enhanced *in vitro* and *in vivo* cell quality that potentially supports a more efficient clinical implementation.

**Keywords:** iPSC, mass manufacture, regenerative cell therapies, clinical translation.

# Abstracts

## THE ROLE OF ALTERED BRANCHED-CHAIN AMINO ACID OXIDATION IN MEDIATING CARDIAC INSULIN RESISTANCE IN HEART FAILURE

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**Background:** Recent studies have shown that cardiac-specific branched-chain aminotransferase (BCATmCardiac<sup>-/-</sup>), which is a maneuver to increase cardiac branched-chain amino acids and lower cardiac branched-chain keto acids (BCKA), enhances insulin-stimulated cardiac glucose oxidation rates while increasing left ventricular (LV) mass. Since stimulating cardiac glucose oxidation is shown to be a cardioprotective approach in heart failure, we hypothesized that lowering BCKAs via BCATm deletion will benefit cardiac function and energy metabolism in the failing heart.

**Methods:** BCATmCardiac<sup>-/-</sup> male mice underwent a sham or transverse aortic constriction (TAC) surgery to induce heart failure. Changes in cardiac function and structure were monitored pre-and post-TAC using echocardiography.

**Results:** Five weeks post-TAC, hearts were collected and perfused as isolated working hearts to assess cardiac energy metabolism. BCATm deletion did not improve cardiac function in the failing hearts compared to the WTCre<sup>+</sup> failing hearts in vivo or ex vivo. However, BCATm deletion exacerbated adverse cardiac hypertrophy, as evidenced by an increase in left ventricular mass in BCATmCardiac<sup>-/-</sup> failing hearts, and triggered the mTOR/P70S6K/4E-BP1 signalling pathway. Despite the lack of functional protection, BCATm deletion did increase insulin-stimulated glucose oxidation rates and cardiac efficiency in the failing hearts, which was associated with enhanced mitochondrial Akt activity. Lowering BCKA levels improves cardiac efficiency in the failing heart via enhancing insulin-stimulated glucose oxidation. However, BCAA accumulation in the failing heart due to BCATm deletion worsens adverse remodelling and offsets any potential beneficial effects of lowering BCKA and improving insulin sensitivity in the failing heart.

**Conclusion:** Lowering BCKA levels could be a potential therapeutic approach to mitigate cardiac insulin resistance in heart failure.

**Keywords:** BCAA, metabolism, heart failure, hypertrophy

# **ABSTRACTS**

Morning Session

## **Oral Presentation**

### **JUNIOR**

Pages 9-14



# Abstracts

## **DIETARY TRIMETHYLAMINE N-OXIDE (TMAO) SUPPLEMENTATIONS ATTENUATES WEIGHT GAIN AND HEPATIC GLUCOSE METABOLISM IN MICE FED A HIGH-FAT DIET**

Fedoruk H, Vetsch B, Mandour B, Lum B, Leonard K, Nelson R, Yue J, Jacobs R

**BACKGROUND:** Trimethylamine N-oxide (TMAO), a choline metabolite, is a product of gut microbiome metabolism that is associated with conflicting positive and negative impacts on glucose metabolism and insulin resistance. The purpose of this study is to determine if, and how, dietary TMAO supplementation impacts glucose metabolism in HFD fed C57BL/6 mice.

**HYPOTHESIS:** Dietary TMAO supplementation will attenuate weight gain and normalize hepatic glucose metabolism in male and female mice.

**METHODS:** 11-week-old male and female C57BL/6 mice were fed a high fat diet (HFD, 42% fat) with or without 0.2% TMAO supplementation for 8 weeks. At weeks 5 and 6, select male and female mice were housed in metabolic cages for 24 hours, and at the beginning of week 8, select male mice were subjected to a glucose tolerance test (GTT) or euglycemic hyperinsulinemic clamps (EGHIC). At week 8, mice were euthanized after fasting, and tissues were collected for analyses.

**RESULTS:** Weight gain was significantly reduced in female mice supplemented with TMAO, likely due to increased whole-body oxygen consumption. We observed no difference in body weight or energy expenditure in male mice. Both male and female mice exhibited improved glucose tolerance following a GTT. Data from EGHIC show no alteration in peripheral glucose uptake following TMAO supplementation; however, insulin-stimulated glucose production was reduced in the TMAO supplemented male mice. There were no significant differences in fasting hepatic or plasma lipid levels, and fasting genes related to insulin signalling, glucose metabolism, or ER stress were unaltered.

**CONCLUSIONS:** Dietary TMAO supplementation may be beneficial for attenuating weight gain (females) and hepatic glucose metabolism (both sexes) in mice fed a HFD. Further research is warranted to determine the metabolic effects of TMAO in an obesogenic state.

**Funding:** NSERC, Alberta Diabetes Institute

**Keywords:** TMAO, choline, glucose metabolism, insulin resistance

# Abstracts

## **HYPOTHALAMIC GLUCAGON INFUSION REGULATES HEPATIC TRIGLYCERIDE SECRETION**

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**Background:** In addition to regulating glucose homeostasis, glucagon is involved in hepatic lipid metabolism. Glucagon activates its receptor (GCGR) in the liver to affect hepatic triglyceride, fatty acid, and cholesterol metabolism. Increased circulating glucagon reduces hepatic lipoprotein production, triglyceride secretion, and plasma triglycerides. Glucagon also acts in the mediobasal hypothalamus (MBH) to modulate hepatic glucose metabolism and appetite. The MBH is a brain region which senses nutrient and hormone to coordinate metabolic homeostasis, including lipid metabolism. However, whether glucagon acts in the MBH to affect hepatic triglyceride secretion and plasma triglyceride levels in healthy and high-fat diet (HFD)-induced hyperlipidemic animals remains unknown. Hence, in this study we examined if direct glucagon infusion into the MBH modulates hepatic triglyceride secretion.

**Methods:** Stereotaxic MBH cannulation and vascular catheterizations allowed for direct MBH infusions, intravenous injections, and blood sampling in Sprague Dawley rats. Plasma TGs were measured in 10h-fasted rats after intravenous poloxamer injection with concurrent MBH infusions. Liver tissue enzymes were analyzed via western blot analyses.

**Results:** In regular chow-fed rats (RC), MBH glucagon decreased TG secretion compared to MBH vehicle controls. This was mediated via GCGR and protein kinase A (PKA) since pharmacological and genetic inhibition of GCGR, or concurrent PKA inhibitor infusion, selectively in the MBH, blocked the TG-lowering effects of MBH glucagon. Interestingly, both MBH glucagon and MBH PKA activation lowered TG secretion in HFD-induced hyperlipidemic animals. However, MBH glucagon did not affect TG content or lipogenic protein levels of MTP, FAS, or pACC:ACC in livers of RC and HFD rats compared to their MBH vehicle controls. Of note, plasma FFA was decreased in HFD rats that received MBH glucagon (vs HFD MBH vehicle).

**Conclusions:** Hypothalamic glucagon modulates hepatic TG secretion, and activating hypothalamic glucagon signalling improves lipid metabolism in hyperlipidemic rats. These findings may provide insight on lowering lipids in hyperlipidemia.

**Keywords:** Glucagon, Hypothalamus, Liver, Triglyceride Secretion

# Abstracts

## **FIBER SUPPLEMENTATION AND METFORMIN COMBINATION THERAPY IN ADOLESCENTS WITH SEVERE OBESITY AND INSULIN RESISTANCE: INTERACTIONS WITH THE GUT MICROBIOME: PROGRESS AND CHALLENGES**

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**Background:** Adolescents with obesity have a higher risk of developing insulin resistance (IR), and early onset of type 2 diabetes mellitus (T2DM). Conventional lifestyle interventions (i.e., diet and physical activity) and pharmacotherapy with metformin (MET) alone show limited effectiveness. However, combining MET with fermentable fibers, mediated by composition and metabolic function of the gut microbiome, may enhance glucose tolerance (GT) and delay T2DM progression. This pilot study aims to assess the use and acceptability of MET and fermentable fiber alone and in combination on reducing IR in adolescents with obesity.

**Methods:** This pilot study uses a parallel, three-arm, double-blind, randomized controlled trial design. A total of 30, 12-18-year-olds with obesity, IR (homeostatic model assessment of insulin resistance [HOMA-IR] >3.16), and positive family history of T2DM are being randomized to receive either MET (n=10), fermentable fibers (n=10), or MET + fiber combination (n=10) for 12 months. Data collection is occurring at baseline, 1-, 3-, 6-, 9-, and 12- months post-baseline. The primary outcome being assessed is change in IR estimated by HOMA-IR. Other outcomes of interest include the use and acceptability of the intervention, recruitment and retention rates, gastrointestinal tolerance to the intervention, changes in the Matsuda index, oral disposition index, and body composition.

**Preliminary Results:** As of September 2022, research funding, research ethics, and Health Canada approvals including clinical site initiation for this study have been received. To date, 63 eligible adolescents have been contacted for recruitment at the Pediatric Centre for Weight and Health in Edmonton, AB, Canada. Of 23 screened adolescents, 4 participants (ages 13-16 years) were enrolled and randomized to one of three arms and will continue the intervention for 12 months. Baseline characteristics collected include mean HOMA-IR of 7.71, body composition values of 40.9% mean percent fat mass, and 59.1% mean percent fat-free mass. Recruitment and data collection are ongoing.

**Conclusions:** Findings from this study will inform a large-scale randomized controlled trial aimed to elucidate the metabolic effects of combined MET and fermentable fiber on GT and provide insight into the role of the gut microbiome as a therapeutic target to prevent T2DM. Recruitment is slow due to the pandemic, and efforts to boost recruitment are being made.

**Keywords:** fermentable fibers, metformin, adolescents, obesity, insulin resistance.



# Abstracts

## **EXPLORING LOCAL IMMUNE MODULATION WITH RAPAMYCIN-ELUTING MICELLES TO PRESERVE ISLET GRAFT FUNCTION IN MICE**

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**Background:** Islet transplantation is an effective way for a subset of people with type 1 diabetes to achieve insulin independence; however, lifelong systemic immunosuppression required to subvert the immune response remains a significant barrier in patient inclusion. Herein, we explore the use of a localized drug delivery system to preserve islet allograft function, reducing the need for toxic systemic immunosuppression. Poly(lactic-co-glycolic acid) (PLGA) is an FDA-approved biomaterial that can form micelles that elute drugs. Rapamycin (rapa) is an immunosuppressant used in clinical islet transplantation, and its hydrophobic properties makes it an ideal candidate for PLGA micelles encapsulation. We hypothesize that this localized rapa-eluting system will subvert the immune response, promoting long-term durable islet function in murine allotransplants.

**Methods:** Rapa-eluting micelles were fabricated and characterized for encapsulation efficiency, morphology, and *in vitro* release kinetics. *In vitro* function of human islets incubated 24h with therapeutic doses of rapa-micelles was assessed with the seahorse XFe24 assay. We examined immune-independent effects by co-transplanting syngeneic islets with rapa-micelles under the kidney capsule of streptozotocin-induced diabetic mice. Utilizing a fully major histocompatibility complex-mismatch murine islet allograft model, the efficacy of rapa-micelles in promoting durable allograft function was examined through non-fasted blood glucose readings and fasted intra-peritoneal glucose tolerance test.

**Results:** Sustained *in vitro* drug release was observed over 35d with stable pH and, moreover, human islets co-cultured with rapa-micelles for 24h had comparable *in vitro* mitochondrial functions to controls. Conversely, islets from the same donor incubated in a therapeutic rapa dose (25 nM) had a blunted glucose-stimulated and ATP-linked respiration. Syngeneic islets co-transplanted with 0.2 mg/kg rapa-micelles (n=8) demonstrated partial graft function with 38% remaining euglycemic at 36d posttransplant, while all 0.1 mg/kg rapa-micelle recipients (n=3) remained euglycemic with similar glucose tolerance to controls. Ongoing murine allotransplants co-localized with 0.1 mg/kg rapa-micelles have prolong function by ~2x compared to empty micelles. At 65d posttransplant, 100% rapa-micelle + acute CTLA4-Ig (n=4) remained euglycemic as opposed to 38% empty micelle + acute CTLA4-Ig (n=8).

**Conclusion:** Co-transplanting 0.1 mg/kg dose rapa-micelles appears to prolong islet allograft function and may be a promising combination therapy with acute CTLA4-Ig treatment.

**Keywords:** Islet transplantation, Biomaterials, Localized immunosuppression



# Abstracts

## **IMMUNOPHENOTYPIC CHARACTERIZATION OF DENDRITIC CELLS IN INDIVIDUALS WITH OBESITY AND VARYING LEVELS OF GLYCEMIA**

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**Background:** Obesity and dysglycemia are associated with immune dysfunction and chronic systemic inflammation in humans. Yet, it is unclear if this effect is most related to adiposity, diet, glycemia, or a combination of these factors. Though multi-factorial, obesity-related immune dysfunction may adversely affect the function and phenotype of immune cells. This study aims to establish distinctions in the expression of two subsets of dendritic cells (DCs), myeloid (mDCs) and plasmacytoid (pDCs), in individuals with obesity and normoglycemia (NG), glucose intolerance (GI), or type 2 diabetes (T2D). As DCs are key antigen-presenting cells that initiate adaptive and innate immunity, we hypothesize that immunophenotypic characterization will reveal decreased DCs in those with obesity or T2D, with potential synergistic effects in the presence of both conditions.

**Methods:** Adults 18-70yrs (n=73) were stratified into 4 groups: lean normoglycemic (Lean-NG; n=31), obese with NG (OB-NG; n=16), obese with GI (OB-GI; n=16), and obese with T2D (OB-T2D; n=10). Diet was controlled through the 4-week provision of all meals using a standardized, isocaloric North American diet. In whole blood, immune cell phenotypes were assessed by labeling immune cells with fluorescence antibodies prior to analyzing using flow cytometry and FlowJo software. mDCs and pDCs were delineated by the respective proportion of single cells expressing HLA-DR+CD11c+CD123- or HLA-DR+CD11c-CD123+. mDCs and pDCs expressing the activation marker CD273+ were also quantified.

**Results:** There were no significant differences between groups for the proportion of mDCs or pDCs at baseline and post-intervention (all  $p > 0.05$ ). All groups likewise saw no diet effect on the proportion of mDCs or pDCs after 4 weeks (all  $p > 0.05$ ). Interestingly, the proportion of pDCs expressing CD273+ significantly decreased in the OB-GI ( $p = 0.01$ ), whereas the OB-NG ( $p = 0.05$ ) and OB-T2D ( $p = 0.06$ ) group did not reach statistical significance.

**Conclusion:** Obesity and glycemia did not appear to affect the proportion of mDCs or pDCs. However, the significant decrease in activated pDCs in the OB-GI group may be attributed to the 4-week consumption of a standardized and isocaloric North American diet.

**Keywords:** Dendritic cells, flow cytometry, immunology, controlled feeding study, obesity

# Abstracts

## **BLOOD GLUCOSE RESPONSE TO MORNING FASTED RESISTANCE EXERCISE IS MORE CONSISTENT THAN POSTPRANDIAL EXERCISE IN ADULTS WITH TYPE 1 DIABETES**

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**Background:** Physical activity provides numerous health benefits for those with type 1 diabetes including increased longevity and a decreased risk of diabetes-related complications. However, physical activity complicates blood glucose management. The primary barrier to physical activity is fear of hypoglycemia, which can be fatal if not properly treated. A secondary barrier is the sense of loss of control over blood glucose levels. This study hypothesized that interstitial glucose trends, measured by continuous glucose monitoring (CGM) would be more consistent following morning fasted resistance exercise (RE) compared to the same exercise performed in the afternoon in a postprandial state.

**Methods:** Five participants (3F/2M; mean  $\pm$  SD: age =  $29 \pm 11.3$  years; BMI =  $27.4 \pm 3.8$  kg·m<sup>-2</sup>; diabetes duration =  $19.4 \pm 6.7$  years; HbA1c =  $7.5 \pm 0.7\%$ ) completed a standardized RE protocol three times in the morning while in a fasted state and three times in the afternoon in a fed state in random order. Interstitial glucose was recorded during activity and for 24 hours post exercise using a Dexcom G6 (Dexcom, San Diego, CA) CGM. Data were assessed visually for consistency in trajectory (increase/decrease) spanning 6 hours post exercise.

**Results:** For 13 of 15 morning fasted RE sessions, participants experienced an increase in interstitial glucose concentrations immediately post-exercise. A similar increase was only experienced in five of 15 afternoon tests. Hyperglycemia (CGM glucose > 10 mmol/L) was more frequent early post-exercise after morning fasted RE, with four of five participants reaching hyperglycemia consistently after all three morning sessions. In contrast, hyperglycemia occurred later (within six hours) and less consistently (three of five participants) following afternoon fed RE. Hypoglycemia (CGM glucose < 3.9 mmol/L) was present after six of 15 morning sessions within six hours after RE, with one participant experiencing hypoglycemia after every morning session. There were eight instances of hypoglycemia within six hours following afternoon fed RE, with one participant experiencing hypoglycemia within three hours after all afternoon sessions.

**Conclusion:** Morning fasted RE may provide a safer avenue for physical activity because of more predictable post-exercise glycemic trends, and occurrence of hypoglycemia during the waking hours. In contrast, hypoglycemia closer to bedtime as occurred following late-afternoon exercise may be more difficult to manage.

**Keywords:** Type 1 diabetes, weight lifting, prandial status

# **ABSTRACTS**

Afternoon Session

## **Poster Presentation**

### **JUNIOR**

Pages 15-24

# Abstracts

## **A SMALL MOLECULE ACTIVATOR OF LYN IMPROVES THE OUTCOMES OF ISLET TRANSPLANTATION IN MICE**

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**Background:** Islet transplantation can achieve insulin independence in individuals with type 1 diabetes. However, islets derived from multiple donors are often required, and functional beta-cells are lost early after transplantation. There is thus a need for strategies to improve graft survival and function. Our lab has recently characterized Lyn as a critical regulator of beta-cell proliferation and survival. We herein sought to test the hypothesis that pharmacological activation of Lyn improves the outcome of islet transplantation in mice.

**Method:** Male BALB/C islets were isolated and transplanted (marginal mass of 125 islets) into syngeneic diabetic mice recipients under the left kidney capsule. Recipients were thereafter injected intraperitoneally once daily with a specific activator of Lyn (MLR-1023) or vehicle for 7 days. Glucose tolerance was performed on days 8 and 28 post-transplant. The graft-bearing kidneys were also harvested for immunohistochemical analysis.

**Result:** A brief 7-day treatment with MLR-1023 was sufficient to stimulate beta-cell proliferation in islet recipients. However, beta-cell mass was not significantly altered, due to inter-individual variations. MLR-treated mice also displayed improved graft vascularization compared to controls. Remarkably, these results translated into better glucose tolerance in the MLR-treated group compared to controls at day 8, concomitantly with increased insulin secretion. However, the effects of MLR-1023 dissipated 21 days after drug withdrawal.

**Conclusion:** In summary, MLR-1023 could be used in clinical islet transplantation to reduce the islet mass that is required to achieve insulin independence or to accelerate the time to normoglycemia.

**Keywords:** Islet transplantation, Lyn, MLR-1023

# Abstracts

## **DETERMINATION OF FRAILTY STATUS USING DIFFERENT TOOLS IN THE COMMUNITY-DWELLING ADULTS WITH DIABETES MELLITUS AND CHRONIC KIDNEY DISEASE**

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**Background:** Frailty is a physiologic condition in which decreased physiologic reserves and altered bodily functions cause increased vulnerability to adverse health outcomes, such as falls and fractures, and reduced health-related quality of life (HRQoL). Several tools have been used to identify frailty in adults which may result in differences in frailty diagnosis and detection. Three frailty tools were used to identify frailty in a cohort of community-dwelling adults with diabetes mellitus (DM) and chronic kidney disease (CKD).

**Methods:** Community-dwelling adults with DM and CKD (20M/33F) enrolled in a resistance exercise study were evaluated for frailty status using three different tools: Rockwood Clinical Frailty Score (CFS), Fried Phenotype (FP) and Edmonton Frail Scale (EFS). Validated tools to measure body composition (Dual Energy X-ray Absorptiometry DXA), cognition (Mini-Mental State Exam MMSE), mental health (Major Depression Inventory MDI, Short Form Health Survey SF-36, hand grip strength (HG), physical performance (Short Physical Performance Battery [SPPB) and activities of daily life (Modified Barthel Scores).

**Results:** Mean ( $\pm$  SD) age, BMI, DM duration and CKD stage were  $67.6 \pm 7.1$ ,  $32 \pm 5.8$ ,  $14.6 \pm 9.2$  yrs and 2 (1-4), respectively. Frailty was identified in 5.7% (FP), 9.0 % (EFS) and 29% (CFS) of participants, respectively ( $p < 0.05$ ). FP and EFS showed the greatest agreement with frailty determinations with  $> 90\%$  agreement ( $p = 0.22$ ) compared with FP vs CFS and CFS v EFS which had lower levels of agreement ranging between 70-75% ( $p < 0.05$ ). EFS total scores were significantly related to FP concepts related to weight loss, fatigue and slower walking speed ( $p < 0.05$ ), but were not related to concepts of HG or levels of physical activity ( $p > 0.05$ ). SPPB scores were significantly lower in frail participants (by FP and EFS) for gait, balance and total scores ( $p < 0.05$ ). MMSE scores, SF-36 subdomain scores and composite scores for mental health and ADL composite scores were significantly lower in frail vs non-frail participants by all three tools ( $p < 0.05$ ). No differences in measures of lean body mass (lean-height<sup>2</sup>, appendicular lean height<sup>2</sup> or lean body mass) were determined between frail and non-frail participants by all three frailty tools ( $p < 0.05$ ).

**Conclusions:** The prevalence of frailty in community-dwelling adults living with DM and CKD may vary depending upon the tool used to assess for frailty identification. Frailty tools differ in their emphasis related to body composition, physical performance, mental and cognitive health.

**Keywords:** Diabetes, chronic kidney disease, frailty tools, community-dwelling adults.

# Abstracts

## **CARDIAC GLUCOSE OXIDATION IS IMPAIRED IN HEART FAILURE WITH PRESERVED EJECTION FRACTION (HFpEF)**

Sun Q, Güven B, Wagg CS, Oliveira AA, Silver H, Zhang L, Vergara A, Chen B, Ketema E, Karwi QG, Wang F, Dyck JRB, Oudit GY, Lopaschuk GD

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**Background:** Heart failure with preserved ejection fraction (HFpEF) is a debilitating disease that is prevalent in obesity and diabetes. Despite continued efforts, few reliable therapies have proven to be effective in treating HFpEF. While it is well-accepted that HF involves changes in myocardial energetics, it remains unclear whether alterations in cardiac energetics contribute to HFpEF severity. Therefore, the objectives of this study were to define the cardiac energy metabolic profile in HFpEF and then attempt to lessen the severity of HFpEF by improving cardiac energetics.

**Methods:** The first part of the study were conducted on 8-week-old male C57BL/6J mice by subjecting them to an obesity and hypertension HFpEF protocol, where the mice were fed a 60% high fat diet (HFD) and given 0.5 g/of N $\omega$ -nitro-L-arginine methyl ester (L-NAME) in the drinking water for 10 weeks. Isolated working hearts were then perfused with radiolabeled energy substrates to directly measure rates of glucose oxidation, glycolysis, fatty acid oxidation, and ketone oxidation. The second part of the study were conducted on 13-month-old female C57BL/6J mice that went through the same HFpEF protocol as described above. A third intervention group of aged female mice were treated with 40mg/kg/day of pyruvate dehydrogenase inhibitor (PDKi) MMR013 while receiving the HFpEF protocol.

**Results:** HFpEF mice exhibited a significant increase in body weight, glucose intolerance, and elevated blood pressure. Echocardiography revealed that HFpEF mice developed diastolic dysfunction and concentric hypertrophy. In HFpEF mice hearts, glucose oxidation was significantly suppressed, with a parallel increase in fatty acid oxidation. There is a decrease in total ATP production in HFpEF hearts compared to control hearts. The PDKi increased glucose oxidation rates in HFpEF hearts. PDKi treated mice had improved systolic and diastolic function compared to vehicle treated mice. PDKi treatment also improved vascular function, ameliorated hypertension, and improved overall survival rates.

**Conclusion:** The heart becomes metabolically inflexible and energy deficient in HFpEF, due to a prominent decrease in glucose oxidation and simultaneous increase in fatty acid oxidation. Stimulation of cardiac glucose oxidation using PDKi lessened the severity of HFpEF and exerts functional benefits. Therefore, targeting cardiac energy metabolism could be a promising therapeutic approach to treat HFpEF.

**Keywords:** Heart failure with preserved ejection fraction (HFpEF), Cardiac energy metabolism, Glucose oxidation

# Abstracts

## **GLUCOCORTICOID ACTION IN THE NUCLEUS OF THE SOLITARY TRACT AFFECTS HEPATIC VLDL-TG SECRETION**

Boyan Vasilev, Mantash Grewal, Eyram Asem, Randal C. Nelson, Richard Lehner, Jessica T.Y. Yue

University of Alberta

**BACKGROUND:** Elevated levels of circulating triglyceride (TG)-rich very low-density lipoproteins (VLDL-TGs) are associated with increased glucocorticoid (GC) action. GCs have extensive roles in lipid metabolism via direct actions on peripheral organs, including the liver and adipose tissue. However, how GCs modulate lipid metabolism via their actions in the brain is less recognized. The dorsal vagal complex (DVC), which includes the nucleus of the solitary tract (NTS), is an important brain region involved in whole-body metabolism. Here, we aimed to assess how GC signalling in the NTS affects hepatic VLDL-TG secretion.

**HYPOTHESIS:** Direct GC infusion into the NTS stimulates hepatic triglyceride secretion.

**METHODS AND RESULTS:** Male Sprague-Dawley rats underwent stereotaxic NTS bilateral cannulation and vascular catheterizations to enable simultaneous direct NTS infusions, intravenous injections, and blood sampling. VLDL-TG secretion rates were measured in 10h- fasted rats after intravenous poloxamer injection with concurrent NTS infusions. NTS GC infusion stimulated VLDL-TG secretion compared to NTS vehicle controls. Simultaneous NTS infusion with GC receptor (GR) antagonist mifepristone abolished the effects of NTS GCs, demonstrating the requirement of NTS GRs to mediate the lipostimulatory effects of NTS GCs. The NTS GC-induced increase in VLDL-TG was not associated with changes in liver pACC, FAS, or MTP or plasma ApoB48/100. However, plasma FFAs were increased in NTS GC infused rats compared to controls, and this was accompanied by an increase in pHSL:HSL protein levels in white adipose tissue.

**CONCLUSIONS:** We provide evidence that NTS GC action, mediated by NTS GRs, stimulates hepatic VLDL-TG secretion. Increased circulating FFA availability may contribute to the lipostimulatory effects of NTS GCs. Future studies to assess the role of NTS GC action in dyslipidemic models are warranted.

**Funding:** NSERC, Diabetes Canada, Alberta Innovates, FGSR



# Abstracts

## **PRE-DIABETES AND EARLY ATHEROSCLEROTIC CARDIOVASCULAR DISEASE IN YOUNG WOMEN WITH AND WITHOUT POLYCYSTIC OVARY SYNDROME**

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**Background:** Polycystic ovary syndrome (PCOS) is a common reproductive-endocrine disorder that affects 10-15% of women, and is associated with a 2-fold increased risk for diabetes and cardiovascular disease (CVD). Early screening of cardiometabolic risk factors and early atherosclerotic CVD is important in the management and prevention of diabetes and CVD in this high-risk population. The aim of this study was to assess pre-diabetes, atherogenic dyslipidemia and early atherosclerotic CVD in high-risk patients with PCOS.

**Methods:** A case-control study was conducted in PCOS and age-BMI matched controls including assessment of fasting plasma lipids, apoB-lipoproteins and insulin-glucose indices. Ultrasound-speckled echocardiography was used to determine early ACVD (carotid plaque and intimal medial thickness (cIMT)) and cardiac function.

**Results:** PCOS ( $149.6 \pm 16.84$  pmol/l) and BMI-matched controls ( $138.7$  pmol/l) had higher fasting plasma insulin compared to healthy-weight controls ( $38.75$  pmol/l), as well as 75% higher HOMA-IR. Insulin was negatively associated with HDL-C ( $r = -0.45$ ,  $P = 0.002$ ) and SHBG ( $r = -0.37$ ,  $P = 0.018$ ), and positively associated with free testosterone ( $r = 0.43$ ,  $P = 0.005$ ) in PCOS. The incidence of carotid plaque was 4-fold higher and 7-fold higher in PCOS compared to BMI-matched and healthy-weight controls, respectively. cIMT was significantly higher in PCOS and BMI-matched controls. Fasting TG ( $r = 0.50$ ,  $P = 0.0003$ ), non-fasting TG ( $r = 0.42$ ,  $P = 0.003$ ), total apoB ( $r = 0.42$ ,  $P = 0.007$ ), and negatively correlated with HDL-C ( $r = -0.31$ ,  $P = 0.03$ ) in PCOS.

**Conclusion:** Our results showed that high-risk women with and without PCOS have impaired insulin-glucose metabolism, an atherogenic lipid profile and early atherosclerotic CVD. These results highlight early risk screening and management for diabetes and CVD in high-risk women.

**Keywords:** Polycystic Ovary Syndrome, diabetes, atherosclerosis



# Abstracts

## **EXPRESSION OF VASCULAR ENDOTHELIAL CADHERIN AND ENDOTHELIAL CELLS IN DEVELOPING PORCINE ISLETS**

Adnan Black, Kieran Purich, Jenny Kim, Gina Rayat

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**Background:** Transplantation of pig islets can serve as a potential treatment for those with Type 1 diabetes. As per standard protocols, pig islets are isolated and cultured over several days prior to transplantation; however, a large percentage do not survive transplantation. This loss may be attributed to the destruction of islet vascularization during isolation. To better understand trends in pig islet vascularization, we investigated the expression of vascular endothelial (VE) cadherin and endothelial cells over various days of culture.

**Methods:** Pancreases from 1-, 3-, 7-, and 10-day old neonatal pigs were surgically removed. Each pancreas then underwent mechanical (mincing) and enzymatic (collagenase) digestion. Islets were then placed in Ham's F10 culture; media was changed on days 1, 3, 5, and 7, and samples were taken on days 3, 5, and 7 of culture. These samples were processed for RT-qPCR gene analysis, western blot protein analysis, growth factor assays, and immunostaining.

**Results:** When examining VE cadherin, we found gene expression to decrease from days 3 to 7 in culture; this trend was statistically significant in islets from 1- (n=4) and 3- (n=6) day old pigs, but not in islets from 7- (n=5) day old pigs. The protein expression of VE cadherin in 1-, 3-, and 7- (n=4 for each) day old pigs showed no clear trends from day 3 to day 7 in culture; this was visually reinforced by the lack of trends noted through immunohistochemistry staining of day 3 to day 7 islets for 1-, 3-, and 7- (n=3 for each) day old pigs. When examining endothelial cells, a vascular endothelial growth factor (VEGF-A) ELISA was performed to quantify growth factor expression relating to endothelial cell development. This assay determined statistically significant decreases in VEGF-A expression from day 3 (n=7) to day 7 (n=3) in culture for islets from 3-day old pigs as well as from day 3 (n=3) to day 7 (n=7) for islets from 7-day old pigs. We used immunofluorescence staining of CD31 (cluster of differentiation 31) as a marker of endothelial cell development and vWF (von Willebrand factor) as a marker of endothelial dysfunction. CD31 expression visually decreased from day 3 to day 7 of culture (n=3 for each) for both 3- and 7-day old pigs, confirming trends noted by the VEGF-A ELISA. vWF expression visually increased from day 3 to day 7 of culture (n=3 for each) for both 3- and 7-day old pigs, reflecting damage to the endothelium as endothelial cell expression decreased.

**Conclusion:** These results provide a better understanding of the trends of protein and gene expression relating to vascular cell-cell adhesion and overall vascularization in islets as they develop in culture, providing more information as to the best days of culture to transplant islets.

**Keywords:** islet transplantation, VE cadherin, vascularization, VEGF-A, CD31, vWF

# Abstracts

## ENZYMATIC REMOVAL OF ABO-A-ANTIGEN IN A MOUSE MODEL OF ABO-INCOMPATIBLE TRANSPLANTATION

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**Background:** Crossing the ABO blood group barrier in solid organ transplantation (Tx) is usually not performed as this can lead to hyperacute rejection due to preformed natural ABO antibodies. However, due to a lag in ABO antibody production, ABO-incompatible (ABOi) Tx can be safely performed in infants and young children. A reduction in A/B donor antigens may be one approach to allow safe ABOi Tx in older age groups. The utility of FpGalNAc deacetylase and FpGalactominidase (Azymes) to convert blood group A-antigen to H-antigen in an *ex vivo* human lung perfusion model was recently demonstrated. However, as A-glycosyltransferases are constitutively expressed the duration of A-antigen removal remains unclear. A-transgenic (Tg) mice constitutively express A-antigen on vascular endothelium and erythrocytes and have been used to model ABOi Tx. Using this model we assessed A-antigen removal and re-expression following Azyme administration *in vitro* and *in vivo*.

**Methods:** Azyme function was studied using A-Tg BALB/c (n=7) and A-Tg C57BL/6 (n=3) mice (both sexes, 10-44 wk). *In vitro*: Red blood cells (RBC) were assessed for A- and H-antigen expression by hemagglutination at various times (0.5-4 hr) post-Azyme treatment (5-450 µg/mL) of whole blood. *In vivo*: A-Tg mice were injected iv with Azyme (0.4-0.8 mg/kg); blood was sampled at various times and RBC were tested for A-antigen by flow cytometry and for A- and H-antigen by hemagglutination. Heart and lung tissue was harvested at various times (2-96 hr) and assessed for expression of A- and H- antigen by immunohistochemistry.

**Results:** *In vitro*, ≥50 µg/mL Azyme cleaved A-antigen from A-Tg mouse RBC and created H-antigen. *In vivo*, Azyme treatment resulted in the absence of A-antigen and the appearance of H-antigen on RBC up to 2 hr post injection, with detection of A-antigen reappearing after 4 hr. Heart and lung tissue showed a reduction in A-antigen up to 4-hr post-injection.

**Conclusion:** Preliminary data suggest success in using an A-Tg mouse model to evaluate removal and subsequent re-expression of A-antigen after Azyme treatment. *In vivo* Azyme treatment resulted in the complete but temporary conversion of A-antigen to H-antigen on RBC, and partial conversion on tissues. Future studies will assess the efficacy of higher doses of Azymes and the resulting re-expression timing. Clinical application of Azyme technology has the potential to increase expansion of ABOi organ Tx allowing life-saving treatment to individuals who would otherwise be ineligible for Tx and use of donated organs that would otherwise be discarded due to lack of compatible recipients.

**Keywords:** ABO-incompatible transplantation, ABH antigens, mouse model

# Abstracts

## **THE EFFECT OF DAIRY PRODUCTS ON LIVER LIPID ACCUMULATION IN A MOUSE MODEL OF PRE-DIABETES**

Dineli N. Fernando, Emad Yuzbashian, Catherine B. Chan

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**Background:** Non-alcoholic fatty liver disease (NAFLD) is characterized by excess lipid accumulation in the liver and is caused by westernized diets and sedentary lifestyles. Additionally, components of metabolic syndrome such as obesity and insulin resistance are significant risk factors for NAFLD acquisition and progression. Currently, there are no pharmacological treatments for NAFLD; thus, lifestyle interventions are the only option. Recent studies show that dairy products, especially milk, can reduce hepatic lipid accumulation though the exact mechanism remains unknown. Herein, we aim to elucidate the mechanisms by which different types of dairy products, namely milk, cheese, and yogurt, act to improve the hepatic lipid profile of a pre-diabetes mouse model.

**Methods:** 8-week male C57BL/6 mice (N=30) were randomly assigned to a 10% fat low-fat diet (LFD, n=6), and the remainder of the mice were assigned to a 45% fat high-fat diet (HFD, n=24) for 1-week. Then, mice from the HFD group were randomly assigned 6/group: HFD, HFD + milk (M), HFD + yogurt (Y), and HFD + cheese (C). After 8-weeks, body weight was measured, the mice were euthanized, and liver tissues were harvested. Histological analysis was performed on the liver tissues, and morphological information such as lipid droplet count and area were obtained following digital image analysis via ImageJ.

**Results:** A significant reduction of lipid droplet count in the HFD + yogurt group compared to the HFD group was observed. The average area of individual lipid droplets observed in the M, Y, C and LFD groups was significantly lower than in the HFD group. Furthermore, we observed a reduction in the percentage of liver area covered by lipid droplets in all groups compared to the HFD group.

**Conclusions:** We demonstrate that the inclusion of dairy products (milk, yogurt, and cheese) in diets high in fat, similar to westernized diets, can reduce hepatic lipid accumulation in a mouse model of pre-diabetes.

**Keywords:** non-alcoholic fatty liver disease, dairy products, mouse model

# Abstracts

## **THE EFFECT OF IRW (ILE-ARG-TRP) ON LIVER LIPID ACCUMULATION IN OBESE AND INSULIN RESISTANT C56BL/6 MICE.**

Alexandra Knox, Stepheny C. de Campos Zani, Catherine B. Chan

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**Background:** Metabolic syndrome is a highly prevalent condition that encompasses multiple metabolic diseases, including hypertension, type 2 diabetes (T2D), visceral obesity, and nonalcoholic fatty liver disease (NAFLD). T2D is highly associated with insulin resistance, obesity, and inflammation. Thiazolidinediones are peroxisome proliferator- activated receptor gamma (PPAR $\gamma$ ) agonists, and known insulin sensitizers; however, their use has many undesired effects, which preclude their use. Liver steatosis (accumulation of lipids) is a characteristic of NAFLD. Immune infiltration, cell hypertrophy, and fibrosis are additional markers found when NAFLD progresses to nonalcoholic steatohepatitis (NASH). There are currently no pharmacological treatments approved for NAFLD. However, there is promising evidence of bioactive peptides improving other metabolic conditions. IRW is a bioactive peptide derived from egg white that showed antihypertensive activity and improved insulin resistance in rodents. I hypothesize that IRW supplementation will decrease liver triglyceride (TG) content and improve NAFLD morphological characteristics in diet-induced insulin resistant obese mice.

**Methods:** C57BL/6 male mice (5-week-old) were fed high fat diet (HFD) for 6 weeks. Mice were then divided into 3 groups, HFD, HFD+IRW (45mg/Kg BW) and HFD+ROSI (rosiglitazone 2.5 ug/Kg BW) and received their diets for another 8 weeks. One group received low fat diet throughout the 14-week period. The liver was collected and formalin-fixed. Tissue slides were stained with hematoxylin & eosin to investigate NAFLD features, including lipid droplet (LD) size and number, inflammatory foci, and hepatocyte size (n=6). Liver TG was extracted and quantified using a colorimetric kit (n=8).

**Results:** The LFD group had a trend for less LD, had smaller LD, less area covered by LD, and less TG compared to the HFD group. The HFD+ROSI group had a higher LD count and increased TG concentration than HFD and HFD+IRW. HFD+IRW had both smaller LD and less area covered by LD compared to HFD and HFD+ROSI. There were no differences when comparing the number of cells per area, nor inflammatory infiltration.

**Conclusion:** IRW is an antihypertensive peptide with potential to manage metabolic diseases. Unlike rosiglitazone, IRW does not seem to worsen diet induced liver lipid accumulation in obese and insulin resistant mice. In fact, IRW is demonstrating improvements of NAFLD features compared to the HFD control.

**Key Words:** Metabolic syndrome, Bioactive peptides, Non-alcoholic fatty liver disease, Mouse model

# Abstracts

## LOCALIZED IMMUNE CELL DEPLETION TREATMENT IN THE PANCREAS OF NEW ONSET NOD DIABETIC MICE

**Kevin Zhan**, Jiaxin Lin, Hui Huang, Jean Buteau, Colin C. Anderson

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**Background:** Type 1 diabetes (T1D) is an autoimmune disorder primarily mediated by CD4 and CD8 T cells that destroy the pancreatic islet beta cells responsible for insulin production. By suppressing these immune cells in new onset T1D patients, it may be possible to prevent the killing of pancreatic beta cells. However, systemic immunosuppressants target immune cells all around the body which increases susceptibility to infections or cancer. Our aim is to investigate a localized approach to deplete CD8 and CD4 T cells in the pancreas without depleting T cells elsewhere in the body.

**Methods:** Blood was sampled from 12 week old female NOD mice (N=15). Levels of CD4, CD8 $\beta$ , TCR $\beta$ , CD19 before and after local antibody injection were determined using flow cytometry. Blood glucose was also determined before and after injection. Depleting antibodies, anti-CD4, anti-CD8, anti-CD90.2, were injected into the pancreas of 6 mice through the celiac trunk after restriction of blood flow from the hepatic, splenic and gastric arteries. 4 mice were injected with PBS as a control. 3 mice had depleting antibodies intravenously injected through the tail vein. A sham procedure was performed on 2 mice where only blood flow restriction was done. 1 day following surgery, the mice were euthanized. Immunohistology was done on spleen and pancreas tissue using fluorescent antibodies for CD4, CD8, and insulin.

**Results:** The method was successful in delivering depleting antibodies locally to the pancreas. We found a decrease in blood glucose and a depletion in splenic T cells 24 hours post-injection compared to sham and PBS controls. Pancreatic T cells were not fully depleted compared to controls suggesting mechanisms other than T cell depletion may have contributed to the efficacy of the treatment.

**Conclusion:** We believe that this treatment has the potential to slow or reverse type 1 diabetes in new onset patients and contributes to the development of new localized treatments for autoimmune disorders.

**Keywords:** Type 1 diabetes, autoimmunity, T cell depletion

# **ABSTRACTS**

Afternoon Session

## **Oral Presentation**

### **SENIOR**

Pages 25-30

# Abstracts

## **TITLE: ELECTROPHYSIOLOGICAL CHARACTERIZATION OF STEM-CELL DERIVED B-CELLS TO HELP PRODUCE CLINICALLY RELEVANT CELLS FOR TRANSPLANT**

Jasmine Maghera<sup>1</sup>, Xiaoqing Dai<sup>1</sup>, Kevin Salim<sup>2</sup>, Shugo Sasaki<sup>2</sup>, Francis C. Lynn<sup>2</sup>, Patrick E. MacDonald<sup>1\*</sup>

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**Background:** Although significant progress has been made in treating type 1 diabetes with islet transplantation, new cell sources are needed since organ donors remains limited. Stem cell-derived  $\beta$ -cells (SC $\beta$ -cells) offer a promising alternative for cell replacement therapy; however, key characteristics displayed by mature primary human  $\beta$ -cells, such as glucose-regulated excitability and insulin secretion via the exocytosis of secretory granules, remain blunted in SC $\beta$ -cells, reflecting immaturity after cellular differentiation.

**Methods:** We seek to characterize the electrical and secretory machinery responsible for regulation of insulin secretion, comparing SC $\beta$ -cells and primary human  $\beta$ -cells. Single-cell patch-clamp electrophysiology was used to assess the cell size, the activity of ion channels involved in action potential firing, and the fusion of secretory vesicles with the plasma membrane.

**Results:** We found that that stage 6 SC $\beta$ -cells (n=42) are significantly (p<0.0001) larger in cell size than primary  $\beta$ -cells (n=51 from 24 donors), having a 2.47-fold larger cell membrane capacitance. The SC $\beta$ -cells display a 9.15-fold larger (p<0.0001) exocytosis compared with primary  $\beta$ -cells, even when normalized to cell size. This increased exocytosis is paralleled by increased voltage-activated Na<sup>+</sup> currents (2.61-fold increased, p<0.0001) and Ca<sup>2+</sup> (4.61-fold increased, p<0.0001), the latter being mediated mostly by L-type channels.

**Conclusions:** These findings suggest that, although SC $\beta$ -cells act differently compared with primary  $\beta$ -cells, the mechanical machinery responsible for excitability and exocytosis is intact and functional by stage 6 of differentiation. Future studies will examine metabolic differences between derived SC $\beta$ -cells and primary  $\beta$ -cells that reduce glucose sensing and insulin release upstream of this secretory machinery.

**Keyword:** Stem-cell Derived  $\beta$ -cells, Transplantation, Type 1 Diabetes



# Abstracts

## **AWARENESS AND FOLLOW UP HEALTH CARE IS LIMITED FOR WOMEN WITH POLYCYSTIC OVARIAN SYNDROME AT HIGH-RISK FOR DIABETES AND HEART DISEASE**

Michaelann S. Wilke, Beate C. Sydora, Mahua Ghosh, Donna F. Vine.

**Background:** Polycystic Ovarian Syndrome (PCOS) is the most common reproductive-endocrine disorder in women, however it also is associated with high incidence of co-morbidities including diabetes and cardiovascular disease (CVD). Our research shows in Alberta there is a 3-fold higher incidence of diabetes and obesity, as well as dyslipidemia (2-fold) and cardiovascular disease (CVD) (>1.5-fold) in PCOS compared to age-matched controls. In this study we aimed to assess the experience and awareness of women with PCOS regarding their high risk for developing diabetes and CVD.

**Methods:** We conducted an online survey of women residing in Canada and diagnosed with PCOS. Data was collected anonymously via REDCap between January 2021 and July 2022. Answers to questions relating to major health issues and concerns were assessed for awareness, education, and treatment of diabetes and related comorbidities.

**Results:** Data were collected from 195 respondents with an average age of  $33.0 \pm 8.3$  years; the majority of whom ( $n=179$ ) resided in Alberta. Most reported diagnoses of overweight/obesity (62%), high cholesterol (15%) and/or prediabetes or diabetes (16%), in addition to their PCOS diagnosis. Almost three-quarters ( $n=136$ ) of respondents had not been informed about potential long term health complications associated with PCOS. Only 13% were referred to a health professional (of any type) at diagnosis to manage PCOS symptoms or comorbidities, including 6 referrals to an endocrinologist. Only three referrals were to a Registered Dietitian, despite body weight and nutrition concerns for respondents ( $n=147$ ; 75%). Less than half of respondents expressed concerns about insulin resistance, a quarter about Type 2 Diabetes, and only 13% indicated that increased cardiovascular risk factors were a health concern. Follow up care was largely absent or consisted of pharmaceutical treatments such as metformin or birth control, or "being told to lose weight." Most respondents indicated they had difficulty losing weight, but only 12% reported receiving medical care for weight loss; the majority stated that they were not receiving adequate care for any of their health care concerns.

**Conclusions:** Canadian PCOS patients are largely unaware of their elevated risk of diabetes or CVD and related co-morbidities, and are often not referred to other health care professionals. The findings of this work will translate to recommendations for improved clinician and patient education and referral to health care professionals to support prevention of diabetes and CVD in this high-risk population of women with PCOS.

**Keywords:** PCOS, Women's Health, Diabetes, Cardiovascular Disease, Health Care



# Abstracts

## THE EMERGING ROLE OF ALPHA-CELL GLUCAGON-LIKE PEPTIDE-1 (GLP-1)

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**Background:** Glucagon-Like Peptide-1 (GLP-1) is released from intestinal endocrine cells in response to dietary glucose. GLP-1 enhances insulin production and secretion from pancreatic beta-cells, and supports beta-cell health during metabolic stress. In certain conditions, GLP-1 is produced by pancreatic alpha-cells. Alpha-cell GLP-1 acts on neighboring beta-cells to improve their function and survival. We aim to identify the molecular mechanism that promotes GLP-1 production in the pancreas so that we may explore this pathway in future drug discovery.

**Methods:** Alpha-TC1/6 cells are cultured in control conditions (5.5mM glucose + saline vehicle) and proinflammatory conditions (interleukin-6 [IL-6], stromal-derived factor-1 [SDF-1]) for 24-72 hours. We harvest cells and assess changes proglucagon processing gene transcription and protein expression. Similar assays are conducted on FACS sorted human alpha cells from cadaveric organ donors distributed through IsletCore.

**Results:** While 72 hours in hyperglycemia elicits a modest 2-fold increase in *PCSK1* (prohormone convertase 1/3 gene) expression, 72hrs in IL-6 or SDF-1 cause a 16-, and 22-fold increase in gene expression, respectively. Both conditions significantly alter the proglucagon processing environment and enhance GLP-1 production.

**Conclusions:** Proinflammatory stimulation by IL-6 and SDF-1 are strong potentiators of *PCSK1* and *PC1/3* expression in alpha cells. These conditions promote GLP-1 production, although the exact cell-signalling mechanism has yet to be determined.

**Keywords:** alpha-cell, hormone processing, proglucagon, GLP-1

# Abstracts

## **GENERATION AND CHEMICAL ABLATION OF OFF-TARGET CELLS FROM AUTOLOGOUS STEM-CELL DERIVED ISLET CELL PRODUCTS TO TREAT DIABETES.**

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Generation of autologous induced pluripotent stem cell (iPSC)-derived islets (SC-islets) capable to reverse diabetes has the potential for islet transplantation without immunosuppression to treat all forms of diabetes. One major limitation to this approach is the presence of residual off-target cells that produce cystic graft growth or teratomas. Protocol refinement to selectively eliminate contaminating undifferentiated cells in SC-islets is essential and ultimately benefit their clinical utility. Herein, we tested chemical drugs (Aphidicolin (APH)- a replication fork inhibitor), physical (dissociation and re-aggregation of SC-islet clusters) in combination with cryogenic approach for unwanted cell ablation in islet differentiation protocol. Absolute cell composition assessment was performed using flowcytometry and immunohistochemistry to ensure safety, efficiency, and optimal maturity of enriched cell product. Our results with APH treatment at the terminal stage of differentiation resulted in absolute removal of undifferentiated iPSC <1% and promoted endocrine maturation with 55% Pdx1+GP2+ and 84% ChrgA+ Nkx6.1+ cells, compared to conventional protocol with 20% Pdx1+ChrgA+ Nkx6.1+. On the other hand, physical and cryopreservation methods were effective but modestly eliminated residual contaminating off-target cells ~5% iPSC and compromised yield. Since APH alone generated SC-islets containing mature endocrine cells without affecting the yield, we measured >2-fold insulin secretion and improved dynamic glucose stimulated insulin response to high glucose and secreting agent- exendin-4. All together, we believe that implementation of chemical molecules in combination with physical and cryogenic manipulations into current differentiation protocols will greatly advance our efforts in absolute removal of off-target cells to manufacture safe and mature “self” SC-islet products.

# Abstracts

## A NOVEL SMALL-MOLECULE ACTIVATOR OF LYN KINASE FOR THE TREATMENT OF TYPE 1 DIABETES

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**Background:** It is recently known that individuals with long-standing type 1 diabetes (T1D) still have surviving functional  $\beta$ -cells. Thus, strategies to promote  $\beta$ -cell protection/replication should be used in the adjuvant therapy of T1D. Our lab has extensively characterized Lyn kinase as a critical regulator of  $\beta$ -cell mass. We herein hypothesized that MLR1023, a pharmacological activator of Lyn, could stimulate  $\beta$ -cell regeneration and improve glucose control in animal models of T1D.

**Methods:** The effect of MLR1023 was tested in two different models of T1D: non-obese diabetic (NOD) mice and streptozotocin-induced diabetic mice. In brief, NOD and streptozotocin-injected C57BL/6J mice were treated with MLR1023 or vehicle at a dose of 30 mg/kg body weight daily for 7 consecutive days, followed by ipGTT. In vitro, human islets from health donors were treated with cytokines or glucolipotoxicity with MLR1023 or vehicle for 24 hours. The  $\alpha$ - $\beta$ -cell mass, cell proliferation, cell apoptosis and insulinitis were determined by immunohistochemistry or immunofluorescent staining.

**Results:** A short treatment of 7-days with MLR1023, a specific activator of Lyn, was sufficient to improve glucose tolerance, and to induce a 2-fold increase in  $\beta$ -cell mass in diabetic NOD mice. The number of PCNA-positive and TUNEL-positive  $\beta$ -cells highlighted the contribution of both proliferation and apoptosis to  $\beta$ -cell mass expansion. Replication of  $\alpha$ -cells and ductal cells was not altered by MLR1023 treatment, limiting the possibility of off-target effects. Several morphological parameters of “islet health”, including insulinitis scores, were improved by MLR1023. Our results were recapitulated in streptozotocin-diabetic mice, used as a second model of T1D. Conversely, mice with  $\beta$ -cell-specific deletion of Lyn did not respond to MLR1023, confirming the implication of Lyn and the direct action of MLR1023 on  $\beta$ -cells. In isolated human islets, MLR1023 significantly increased  $\beta$ -cell proliferation, and prevented apoptosis induced by cytokines and glucotoxicity, thereby suggesting that MLR1023 could exert similar beneficial actions in humans with T1D.

**Conclusion:** Our study identifies Lyn as a promising target in T1D treatment and small molecule activators of Lyn could be used to delay or cure T1D.

**Keywords:** Lyn, MLR1023,  $\beta$ -cell mass, proliferation, apoptosis

# Abstracts

## **THE KETOGENIC DIET BLUNTS INSULIN-STIMULATED GLUCOSE OXIDATION IN THE FAILING HEART**

Kim L. Ho, Qutuba G. Karwi, Brandon Chen, Faqi Wang, Cory Wagg, Liyan Zhang, Sai Panidarapu, Simran Pherwani, Amanda A. Greenwell, Gavin Oudit, John R. Ussher, Gary D. Lopaschuk

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**Background:** Cardiac metabolism is perturbed in heart failure and is characterized by a shift from mitochondrial oxidative metabolism to glycolysis. Notably, the failing heart relies more on ketones for energy than a healthy heart, an adaptive mechanism that improves the energy-starved status of the failing heart. However, whether this can be implemented therapeutically remains unknown. Therefore, our aim was to determine if increasing ketone delivery to the heart via a ketogenic diet can improve the outcomes of heart failure.

**Methods:** C57BL/6J male mice underwent a sham or left anterior descending coronary artery ligation surgery to induce heart failure. At 2 weeks post-surgery, mice were fed a control or ketogenic diet for 3 weeks. Echocardiography was carried out to assess cardiac function. Next, isolated working hearts were perfused with appropriately 3H or 14C labelled glucose (5 mM), palmitate (0.8 mM), and  $\beta$ -hydroxybutyrate (0.6 mM) to assess metabolism. Lastly, immunoblotting was carried out on collected heart tissue to assess the metabolic protein expression profile.

**Results:** Mice with heart failure exhibited a 56% drop in ejection fraction which was not improved with a ketogenic diet. Similarly, cardiac work was decreased by 53% in isolated working hearts from heart failure mice and not affected by the ketogenic diet. Interestingly, mice fed a ketogenic diet had increased myocardial fatty acid oxidation and decreased glucose oxidation and ketone oxidation rates. The unexpected decrease in ketone oxidation rates was supported by decreased expression of the main ketone oxidative enzyme,  $\beta$ -hydroxybutyrate dehydrogenase 1. Despite increases in fatty acid oxidation, overall TCA cycle activity was not increased with the ketogenic diet. Furthermore, insulin-stimulated glucose oxidation was blunted in mice fed a ketogenic diet regardless of whether they had heart failure or not. Lastly, the ketogenic diet did not affect cardiac oxygen consumption or cardiac work, thus not improving cardiac efficiency.

**Conclusion:** The ketogenic diet results in decreased ketone oxidation, glucose oxidation and increased fatty acid oxidation rates. The ketogenic diet does not increase energy production but rather, causes a shift in reliance to fatty acids for energy. Lastly, the ketogenic diet does not improve cardiac efficiency and blunts insulin-stimulated glucose oxidation. The latter observation suggests that the ketogenic diet causes cardiac insulin resistance.

**Keywords:** cardiac, metabolism, heart failure, ketogenic diet



*Alberta Diabetes*  
**INSTITUTE**

# 2022 RESEARCH DAY

0815-1600 | 1-040 LKS (Oborowsky Degner Seminar Hall) & LKS Foyer

**FRIDAY OCTOBER 28**



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