2020 RESEARCH DAY

November 2 and 3

Monday (Day 1) 0900-1200 | Tuesday (Day 2) 0900-1215

Held Virtually

University of Alberta

KEYNOTE SPEAKER

Lorraine Lipscombe, MDCM, MSc, FRCPC

Associate Professor, Division Director, Endocrinology and Metabolism,
Women’s College, University of Toronto
Program

2020 ADI RESEARCH DAY
Monday, November 2 (Day 1) and Tuesday, November 3 (Day 2)
Held Virtually, University of Alberta

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Leading the World in the Prevention, Treatment and Cure of Diabetes
Welcome to the 2020 Alberta Diabetes Institute Research. 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 will be a little different. With the help of our dedicated ADI Trainee Working Group and ADI Members, Trainees, and administration we have organized an exciting couple of mornings of talks and discussions that will provide an enriching experience for everyone attending.

We are excited to host keynote speaker Dr. Lorraine Lipscombe, Associate Professor, Division Director of Endocrinology and Metabolism at the Women’s College Hospital, University of Toronto. Her talk is entitled *Pregnancy as a window of opportunity to identify and reduce risk of diabetes*. Welcome Lorraine!

Our research day is intended to provide a forum to showcase the research efforts of our **ADI Trainees**. With respect to this research day all abstracts submitted were selected for oral presentation. There are four sessions held over two days with a total of 24 presentations: junior trainees (summer students / MSc students) and senior trainees (PhD / postdoctoral fellows / research associates). Junior trainees have 5 minutes in total (including Q&A) and senior trainees have 10 minutes in total (including Q&A) to present their research.

A special thank you to the ADI Trainee Working Group for their efforts in this year’s ADI Research Day. Also, a big thank you to our volunteer judges, session chairs, and zoom support. Also, thank you to the Alberta Diabetes Foundation, our long-standing funding partner, for their continued efforts in raising money to support our research projects and trainees. Research at the Alberta Diabetes Institute is made possible by your dedication and excellence. Through your efforts, we are ideally positioned to continue to make major advances in the prevention and treatment of diabetes, and ultimately to find a cure. We hope that you will be inspired by your peers to continue to excel in your scientific endeavors and I encourage you to ask questions during both the talks and poster sessions.

Despite the weird and troubling times we are all experiencing right now, I hope everyone is doing well. 2020 will be remembered for obvious reasons, but it should also be remembered and celebrated as the 100th anniversary of Dr. Frederick Banting’s idea, written in his notebook on October 31st 1920, for the discovery of insulin that followed in 1921. The University of Alberta played a key role in this discovery as Dr. James Collip, a UofA Biochemistry Professor, was part of the team in Toronto that purified insulin from pancreatic extracts that led to the first successful treatment of diabetes patients. We should all not only take a moment to acknowledge this incredible achievement, but also we should take credit for being an essential part of improving the lives of those living with diabetes as we work towards a cure. I wish you all the best in your current and future research!

Best Regards and stay safe,

Peter Light, PhD
Director, Alberta Diabetes Institute
Dr. Charles A. Allard Chair in Diabetes Research
Professor of Pharmacology
Dr. Lorraine Lipscombe is an Associate Professor in Medicine, Division of Endocrinology, at University of Toronto, and is cross-appointed at the Institute for Health Policy, Management and Evaluation. She is an endocrinologist and serves as the director of the Division of Endocrinology at Women’s College Hospital, as well as a scientist at the Women’s College Research Institute. Dr. Lorraine Lipscombe received her medical degree from McGill University in 1998. She completed her Internal Medicine training in 2002, her fellowship in Endocrinology and Metabolism in 2003, and a Master's of Science in Clinical Epidemiology in 2005, all at the University of Toronto. Dr. Lipscombe has developed a successful research program in diabetes epidemiology and health services, with a particular focus on diabetes in women. She has published over 100 peer-reviewed articles of her work, and holds a Diabetes Investigator award from Diabetes Canada. Her research has contributed to our understanding of the complex association between diabetes and breast cancer, informing interventions to improve outcomes for patients with both conditions. Dr. Lipscombe is currently leading a clinical trial to evaluate a diabetes prevention program for women with gestational diabetes. She is also the proud mother of 3 spirited children.
# WELCOME – Day 1

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## KEYNOTE SPEAKER

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### BREAK

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## SESSION 1  Chair – Dr. Caroline Richard

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<td>1106-1116</td>
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<td>1118-1128</td>
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*Note to judges – Bushra Anjum moved from Session 2 (Junior Talks – 5 minute presentation) to accommodate class schedule*

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Adjourned until November 3 (Day 2)
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## SESSION 2  Chair – Dr. Jane Yardley

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<td>0919</td>
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<td>0932</td>
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## SESSION 3  Chair – Dr. Andrew Pepper

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<td>1000</td>
<td>Ana Paula PAGANO Prado Lab</td>
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<td>1012</td>
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<td>1048</td>
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## SESSION 4  Chair – Dr. Padma Kaul

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<td>1122-1132</td>
<td>MARFIL-GARZA Braulio</td>
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<td>1134-1144</td>
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<td>1146-1256</td>
<td>POLISHEVSKA Kateryna</td>
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<td>1158-1208</td>
<td>SOSA Carla</td>
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## CLOSING REMARKS

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Prize winners will be notified by email on November 4 and announced on the ADI Update and social media.

**ORAL PRESENTATION AWARDS**

**Session 1 (Senior Trainees – postdocs & research associates)**
- 1 Best Award & 1 Honourable Mention

**Session 2 (Junior Trainees – summer students & MSc)**
- 1 Best Award & 1 Honourable Mention

**Session 3 (Senior Trainees – PhD)**
- 1 Best Award & 1 Honourable Mention

**Session 4 (Senior Trainees – PhD)**
- 1 Best Award & 1 Honourable Mention
2020 ADI RESEARCH DAY

ABSTRACTS

Session 1
BUILDING A COMMON VISION: QUALITY IMPROVEMENT ACROSS 5 DIABETES CENTERS IN THE EDMONTON ZONE

Roseanne O Yeung, Taylor McGuckin, Rukia Swaleh, Tyler W Myroniuk, Denise Campbell-Scherer, Brock Setchell, Liesje Sarnecki, Anna Lam, Peter Senior

Office of Lifelong Learning, Faculty of Medicine and Dentistry, University of Alberta

Background: Five diabetes outpatient clinics provide care in Edmonton. An Edmonton Zone Diabetes Quality Council was formed in 2018, bringing these sites together to improve care delivery. This project established a baseline understanding of the types of patients and services provided across the zone.

Methods: Administrative data was extracted for patients that visited a diabetes center in the Edmonton Zone between March 2017 and December 2018. Descriptive statistics were produced.

Results: 11,714 adult patients, representing 77,782 in-person and remote encounters. Mean age was 41.2 (SD 15.6) years; 68.0% were female. Encounters were by patients with gestational diabetes (GDM) (35.9%), 24.2% with type 1 diabetes (T1DM), and 24.6% with type 2 diabetes (T2DM). Type of diabetes was unclear in 1 out of 6 patient records. Mean HbA1c was 7.7% (SD 2.4). Cardiovascular disease, chronic kidney disease, and dyslipidemia were the main comorbidities identified. Uptake of SGLT2 inhibitors and GLP-1 receptor agonists was 15.1% and 6.3% respectively. There were limitations with data mapping due to the use of real-world administrative databases.

Conclusion: The foundation of quality improvement (QI) is reliable data about the current state. This project illuminates ways to advance QI through providing practice information for reflection.

Keywords: Type 1 Diabetes, Type 2 Diabetes, Gestational Diabetes, Electronic Medical Record, Benchmarking
MOLECULAR MECHANISMS OF GENETIC RISK FOR TYPE 2 DIABETES: A FOCUS ON ZMIZ1

Tamadher A. Alghamdi1, Nancy Smith1, Aliya F. Spigelman1, Nicole A. J. Krentz2, Anna L. Gloyn2,3, Zijie Sun4, Patrick E. MacDonald1

1Department of Pharmacology and Alberta Diabetes Institute, University of Alberta, Edmonton, AB, Canada
2Division of Endocrinology, Department of Pediatrics, Stanford University School of Medicine, Stanford, CA, USA
3Stanford Diabetes Research Centre, Stanford University, Stanford, CA, USA
4Beckman Research Institute, City of Hope, Duarte, CA, USA

Background: Impaired insulin-secretion from pancreatic beta-cells is a hallmark of type 2 diabetes (T2D). Over the past decade, genome wide association studies (GWAS) have identified over 400 genetic signals at more than 250 loci associated with predisposition to T2D with the majority conferring their risk through modulation of insulin secretion. We have previously integrated T2D -GWAS with transcript expression data from human islets, identifying ZMIZ1 as a casual transcript influencing T2D predisposition. ZMIZ1 is a little -studied PIAS-family protein demonstrated to be a transcriptional co-regulator, binding with p53 and the androgen receptor. The role of ZMIZ1 in islet function and glucose homeostasis is poorly understood. Here, we investigated the phenotypic effects of ZMIZ1 absence in a beta-cell-specific Zmiz1 knockout (bZmiz1-KO) mice.

Methods: Female and male bZmiz1-KO mice were generated by crossing a Zmiz1-floxed line with the Ins1Cre knock-in. These mice and their control littersmates were studied at 12 weeks of age and put on either chow diet (CD) or high fat diet (HFD) for 8 weeks. Glucose homeostasis was assessed in vivo by glucose tolerance test and pancreas tissues were collected to assess beta cell mass by immunostaining for insulin. RNA-seq was performed to assess pancreatic islet transcriptome in bZmiz1-KO mice.

Results: Both male and female bZmiz1-KO mice are glucose intolerant and have reduced circulating insulin. After an 8-week HFD, bZmiz1-KO mice become overtly diabetic with high fasting glucose and severely impaired oral glucose tolerance. RNA-seq analysis showed more than 300 differentially expressed genes and ISMARA analysis hints towards an implication for RFX transcription factor family known to play a role in islet development and beta cell function. Indeed, male bZmiz1-KO mice appear particularly sensitive to HFD and our data suggest that an impaired beta-cell mass in the male bZmiz1-KO mice after HFD may underlie this phenotype. These data underscore the role of ZMIZ1 in modulating insulin secretion and glucose homeostasis and in vitro functional assessment of islets will provide mechanistic insight.

Conclusion: Zmiz1 plays a role in glucose homeostasis and unraveling an unidentified role for ZMIZ1 in beta cells in health and diabetes may potentially lead to exploration of new molecular mechanisms controlling islet function in diabetes.

Key words: ZMIZ1, beta cells, islet, type 2 diabetes.
A SMALL MOLECULE ACTIVATOR OF LYN IMPROVES GLUCOSE TOLERANCE AND BETA-CELL MASS IN T1D

Hui Huang, Qian Wang, Jean Buteau

Department of Agricultural, Food and Nutritional Science (AFNS), University of Alberta

Background: MLR1023 is a small molecule activator of Lyn and a candidate anti-diabetes medication. Indeed, in phase 2 clinical trials, MLR1023 showed potent glucose-lowering activity in participants with type 2 diabetic. However, the exact mechanisms by which MLR1023 exerts its action remained unknown. Using genetically-engineered mice, our lab has shown that Lyn is a critical regulator of beta-cell mass and function. Consistently, pharmacological activation of Lyn with MLR1023 induced β-cell proliferation and survival, resulting in beta-cell mass expansion. Thus, we herein hypothesized that MLR1023 could improve glucose tolerance and β-cell mass in type 1 diabetes.

Methods: We sought to test the effects of MLR1023 in two different models of T1D: non-obese diabetic (NOD) mice and streptozotocin-induced diabetic mice. In brief, NOD mice were treated with/without MLR1023 at a dose of 30 mg/kg body weight daily for 7 consecutive days after the apparition of hyperglycemia (13.9 mM glucose for 2 consecutive days). C57BL/6J mice were injected with a single moderate dose of streptozotocin (80mg/kg) before MLR1023 treatments. At the end of treatments, mice were subjected to ipGTT and pancreases were harvested for determination of β-cell mass, alpha-cell mass, proliferation, and survival.

Results: NOD mice treated with MLR1023 exhibited improved glucose tolerance and lower fasting blood glucose, consistent with the results obtained in type 2 diabetic models. MLR1023-treated mice showed a 2-fold increase in beta-cell mass vs controls, whereas α-cell mass did not change significantly. Notably, there was a significant increase in the number of large islets in the MLR1023-treated groups. Increased number of PCNA-positive β-cells indicated a contribution of β-cell proliferation to the effects of MLR1023. Although apoptotic beta-cells are too scarce to do any meaningful analysis, morphological assessment of islets suggested a protective effect of MLR1023 in T1D models.

Conclusion: MLR1023 protects residual β-cell mass and promotes beta-cell regeneration in models of T1D, thereby delaying disease progression. Our study identifies Lyn as a promising target in T1D treatment.

Keywords: Lyn, MLR1023, β-cell mass, proliferation
AUTOLOGOUS HUMAN IPSC-DERIVED ISLET GENERATION AND SCALE-UP TO RESTORE NORMOGLYCEMIA AND REVERSE DIABETES.

Nidheesh Dadheech, Rena Pawlick, Braulio Marfil Garza, Sandhya Sapkota, Mario Abelardo Bermúdez de León, and AM James Shapiro.

Alberta Diabetes Institute, Department of Surgery, University of Alberta.

Background: Methods to scale-up and produce reliable pluripotential stem cell-(PSC) derived islets is a current limitation for diabetes cell therapy. In this study, we tested vertical wheel-based 3D bioreactor systems for stem cell (SC)-Islet mass production.

Method: Healthy and diabetic patient-derived iPSC lines were created using Sendai virus, expanded, and differentiated into functional β-like cells using vertical-wheel 3D bioreactors. Aggregated SC-Islets were transplanted into immunodeficient mice to treat diabetes.

Results: Human iPSC lines showed normal karyotyping and PSC markers (92.8±1.0% Tra1-60). Within bioreactors, iPSCs (2E4±0.5 cells/ml) aggregated and expanded by 16.8±1.2 and 47.2±2.5 fold following 4 and 6 days of fed-batch suspension culture, respectively. We assessed the iPSC aggregate growth rate with an average aggregate size of 300±50 µm at day-4. Scale up to three hundred milliliter suspension culture in the bioreactor allowed for effective differentiation of iPSCs into stages (S) 2-7 cells. Differentiated cells assessed at S-2 (63% CXCR4/CD117), S-4 (80% Pdx1, 25% Nkx6.1), and S-7 (70% Ins, 12% Gcg, and 1-5% Sst) with flowcytometry. In-vitro static insulin secretion assay (30 SC-Islet clusters) showed an approximate 2.5 fold-insulin release and phase I and II insulin secretion under dynamic islet perifusion. Immunofluorescence of SC-Islets identified endocrine type expression of Ins, Gcg, Sst, Pp, and ChrgA with much less exocrine cells (Ck19, amylase). Diabetic SCID-Beige mice (n=7) transplanted with 5E6 (S-4 or -7) cells attained normoglycemia (5.8±0.5mM Glu) within 60 days. 14-week transplanted mice presented normal glucose tolerance and stimulated human c-peptide release (0.8ng/ml). Graft histology (d100) confirmed in-vivo maturation with all pancreatic hormones (no polyhormonal cells) and enhanced engraftment.

Conclusion: Scale-up of iPSCs while maintaining naïve pluripotency is effective utilizing 3D suspension culture bioreactors. With an established endocrine differentiation protocol, 3D bioreactors can successfully differentiate and scale-up iPSC-Islets that mature in-vivo and reverse diabetes in mice.

Keywords: Human iPSC, Stem Cells, β-cell Regeneration, Diabetes.
UNDERSTANDING THE BIGGER PICTURE: EXPERIENCES OF VULNERABLE IMMIGRANT POPULATIONS LIVING WITH DIABETES AND OBESITY

Nicole N. Ofosu1, Thea Luig1, 2, Naureen Mumtaz1, Yvonne Chiu6, Roseanne O. Yeung5, 3, Karen K. Lee5, Denise Campbell-Scherer1, 2, 5

1Department of Family Medicine, 2Physician Learning Program, 3Division of Endocrinology & Metabolism, 4Division of Preventive Medicine, Faculty of Medicine & Dentistry, University of Alberta | 5Alberta Diabetes Institute | 6Multicultural Health Brokers Cooperative

Background: People living with obesity and type 2 diabetes want and need care that is tailored to their specific context in order to be able to make changes to improve their health. However, developing contextually appropriate interventions for people living with these conditions in vulnerable ethnocultural newcomer communities is a highly complex problem that requires a deep understanding of their unique situation and context. The purpose of this research is to understand the lived experiences and, healthcare and service gaps faced by people living with diabetes and/or obesity in these communities.

Methods: A collaborative, participatory approach involving a partnership with the Multicultural Health Brokers (MCHB) Cooperative who support diverse ethnocultural communities. Using qualitative research methodology, we generated data through interviews and focus groups with people living with diabetes and/or obesity from several ethnocultural communities, namely South Sudan, Somali, Eritrean, Chinese, French-speaking African, South Asian, and Filipino. Together with the MCHB partners, we are conducting a collaborative data analysis, using thematic analysis.

Results: Emerging findings show a need for emplacement across the board for all newcomers to Canada. Emplacement refers to the process of becoming oriented in a new environment, being able to adapt, make a living, understand the new environment, and navigate it to sustain one's self. However, the magnitude of one's emplacement needs is affected by their immigration route/status (e.g. refugee, temporary foreign worker, skilled worker, etc.) and its attendant experiences, as well as their post immigration realities. Poverty/financial constraints, difficult family/social situations, cultural distance (including language barrier) were key post immigration realities impacting people's ability to fully utilize the healthcare services available. These factors translated into challenges such as a perceived burden of treatment of managing diabetes and obesity, and difficulties navigating the patient-provider relationship.

Conclusion: The ability of people living with diabetes and/or obesity from vulnerable ethnocultural communities to adequately utilize healthcare and services is largely impacted by their contextual conditions. A relational approach in patient-provider interactions that considers patient context and its impact on their health and ability to adequately utilize the services available may be helpful in addressing the health care gaps.

Key words: vulnerable immigrant population, primary care, diabetes, obesity, participatory
EXPRESSION OF DISTINCT TRANSCRIPTOMIC MARKER GENES INFLUENCE ELECTROPHYSIOLOGICAL PROPERTIES OF HUMAN ISLET CELLS

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Background: Pancreatic α and β cells regulate circulating glucose levels by releasing glucagon and insulin, respectively, which are disrupted in diabetes. These electrically excitable cells are functionally heterogeneous, and much attention has been devoted to identifying the underlying electrophysiological, metabolic, and transcriptomic diversity using animal models, and to a lesser extent, human cells. We recently presented data using linked electrophysiological profiling and single-cell RNA sequencing (patch-seq) in human islet cells that showed, among other things, heterogeneity of Na+ channel currents amongst sub-populations of α and β cells. This suggests that islet cell sub-populations differ in their inherent excitability, although this was not tested directly. We are now investigating excitability and action potential firing of single human islet cells coupled with single-cell RT-qPCR assessment of cell-type and sub-population specific marker gene expression.

Methods: Islets were isolated from human pancreas and dispersed into single cells for whole-cell patch clamp measurement of membrane properties. Following electrophysiological measurement, single cells were collected into lysis buffer, and cDNA synthesis, preamplification, and qPCR was performed using a commercial kit and validated assays.

Results: Our preliminary results validate the heterogenous expression of markers such as RBP4 and LOXL4 in human α and β cells. These cell sub-populations exhibit distinct resting and active membrane properties, with LOXL4+ α cells and RBP4- β cells showing increased excitability. We also found considerable heterogeneity in resting membrane potentials, action potential amplitudes, and other parameters within each cell type. Finally, we also show that our experimental approach is applicable in adult human pancreatic slices, allowing electrophysiological characterization of islet cells in their native microenvironment and mapping of functions to known transcriptomic markers.

Conclusion: Heterogeneity of marker gene expression in human pancreatic islet α and β cells give rise to cell sub-populations with varying electrophysiological properties.

Key Words: islet, alpha cells, beta cells, heterogeneity, membrane excitability, gene expression

ADI Research Day 2020
THE ROLE OF SEX AND THE MICROBIOME IN PRODUCTION OF 'NATURAL' ANTIBODIES: IMPACT ON ABO ANTIBODIES IN A MOUSE MODEL

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Background: ABO histo-blood group incompatibility is a barrier in solid organ transplant due to ‘natural’ preformed ABO antibodies (Ab). The ABH glycan microarray, developed in the West lab, determines the isotype (IgM/IgG) and ABH subtype specificity (subtypes I-VI) of natural ABO Abs in a mouse model. We previously found that BALB/c (BALB) mice produce Abs specific to subtypes III/IV A-antigens whereas specificity to subtype II A-antigens were low/absent. Females, compared to males, had significantly higher levels of anti-A Abs and showed a distinct shift in anti-A Ab production from IgM to IgG isotype at about the age of sexual maturity (6-9 wks). Natural ABO Abs may develop due to cross-reactivity with components of the gut microbiome. To test this hypothesis, we examined serum ABO Ab levels in germ-free (GF) and conventionally-housed (conv) male and female mice of different ages.

Methods: GF mice and conv mice included the inbred strains C57BL/6 (B6) (females/males, n=10/10) and BALB (females/males, n=10/10), and the outbred strain Swiss Webster (SW) (females/males, n=4/6). Plasma obtained from tail bleeds at different ages was assessed by ABH glycan microarray for ABO Ab subtype specificity and isotype.

Results: Anti-A and anti-B Abs were present in GF B6, BALB and SW mice at levels similar to that of conv mice. At 4-wks of age, IgG (but not IgM) anti-A Abs were detected in both sexes at levels similar to that of older (12 wks) female mice. Anti-A Abs were present in males >8-wks of age, however these were at low levels vs females and remained mostly IgM. In females, anti-A Abs were mostly IgG isotype at 4-wks of age, predominately IgM isotype at 8-wks of age, and then shifted to mostly IgG isotype by 12-wks of age. Anti-B Abs were detected in both sexes by 8-wks of age, remained mostly IgM, and were present at lower levels vs anti-A Abs. Most natural anti-A Abs, in GF or conv mice, were specific to subtypes III/IV whereas Abs specific to subtype II antigens were low/absent.

Conclusion: The distinct IgM to IgG anti-A Ab class-switching in female mice at about sexual maturity (age 8 wks) may provide early immunity to pups through passive transfer of IgG anti-A Ab during pregnancy. Detection of natural anti-A Abs in GF mice combined with higher levels of natural anti-A Ab in females vs males suggests a unique sex-dependent, alternative mechanism of natural ABO Ab production than cross-reactivity with gut microbiome antigens.

Keywords: Germ-free, natural ABO antibody, sex differences, ABO histo-blood group antigen
THE ROLE OF NECROPTOSIS IN β-CELL LOSS FOLLOWING ISLET CELL TRANSPLANTATION

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**Background:** Intrahepatic islet cell transplantation currently results in an estimated 70% loss of transplanted β-cell mass within 24 hours of transplant, primarily due to instant blood mediated inflammatory reactions (IBMIR). Necroptosis, a programmed and regulated form of necrotic cell death, occurs following cell damage or inflammation. The necroptosis signaling cascade requires the involvement of receptor interaction protein kinase 1 and 3 (RIPK1 and RIPK3, respectively), which form the necrosome. The goal of this project is to determine the function of necroptosis in β-cells survival, following islet cell transplantation. It is hypothesized that inhibition of RIPK1 and RIPK3 in islets, and subsequently, inhibition of the necrosome formation, will prevent necroptosis from occurring post-transplant. This will inhibit cell death and improve islet engraftment.

**Methods:** Human islets, neonatal porcine islets, and MIN6 cells were co-cultured in +/- necrostatin-1s, +/- necrostatin-1, and necrostatin-1i for 24 and 48 hours at 37°C and 5% CO2, to determine the safety, efficacy, and optimal dose of these inhibitors. Nec-1s is an inhibitor of RIPK3, Nec-1 is an inhibitor of both RIPK1 and RIPK3, and Nec-1i is an inactive control. Following incubation, 2-hour exposure of H2O2 (400uM) initiated cell death. In vitro islet function was assessed by oxygen consumption rate, glucose stimulated insulin secretion, and cell membrane integrity 24 hours after culture and post-H2O2 stimulation.

**Results:** Preliminary data suggests that Nec-1s is non-toxic to islets and cells at concentrations less than 400uM. Both Nec-1 and Nec-1s may protect against H2O2 induced cell death.

**Conclusions:** Inhibition of necroptosis may improve islet engraftment by conferring protection to the islet cells following transplantation, leading to an increased rate of cell survival.

**Keywords:** islet cell transplantation, necroptosis, regulated necrosis, IBMIR

ADI Research Day 2020
EXPLORING ALPHA-CELL HETEROGENEITY THROUGH MULTI-DIMENSIONAL APPROACHES

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Background: As big data becomes more prevalent with expanding repertories of data sets, the necessity for efficient analysis is growing. Machine learning is one way to handle and analyze large cohorts of data. This ranges from simple algorithms such as regressions, to more complex training algorithms such as ensemble learning. Furthermore, whilst machine learning can facilitate and enhance hypothesis driven questions, it can also be used to identify trends in existing data, allowing de novo hypothesis generation. This increases the value of data cohorts, as data collected to serve a set of predetermined hypotheses can also be used to generate and explore new questions. Our group continues to expand a growing cohort of single cell electrical and RNA-sequencing data obtained from human islet donors with no diabetes (ND), type 1 diabetes (T1D), or type 2 diabetes (T2D). Machine learning approaches applied to this data have allowed us to not only observe how pancreatic endocrine cells differ between ND, T1D, and T2D donors, but also aid in identifying other aspects such as isolation techniques and handling that affect our measured phenotyping.

Methods: Human donor islets were obtained through the University of Alberta IsletCore. Dispersion of whole islets to single cell were performed enzymatically with trypsin. Single cell functional assays performed include electrophysiology by whole-cell patc-clamp combined with single-cell transcriptomic profiling via Smart-Seq2 (patch-seq). Machine learning approaches used to analyze the data include linear regression, multiple regression, and ensemble learning with boosting, carried out in Python. Training data for ensemble learning included ND cells from donors age 20-70, BMI 18.5-30.03, with cold ischemia times </= 20hrs.

Results: Linear regression analysis of alpha-cell size and transcriptome at single cell resolution revealed transcripts and pathways which may contribute to impaired glucagon regulation in T2D, including the expression of immunology-related surface markers. To study the potential impact of additional donor and tissue handling parameters on alpha-cell function, multiple regression analysis revealed that the impact of cell pre-incubation on alpha-cell electrical properties was greater in cells from ND as compared to T2D donors; while in T2D alpha-cells the years with diabetes, BMI, and HbA1c showed significant correlations with functional properties. Finally, ensemble learning revealed that the population of alpha-cells displaying canonical alpha-cell behaviour is significantly reduced in T2D donors.

Conclusions: Whilst still in its preliminary phase for this analysis, machine learning approaches are currently demonstrating their usefulness in discerning transcriptomes and pathways, cell identity predictions, and in linking transcriptomic data to cellular function.

Key Words: Single-Cell Analyses, Machine Learning, Transcriptomics, Human Donors

ADI Research Day 2020
ROLE OF INTESTINAL DE NOVO PHOSPHOTIDYLCHOLINE SYNTHESIS IN LIPID METABOLISM

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Background: Phosphatidylcholine (PC) is important for the structural integrity of mammalian membranes and is the primary phospholipid in bile and plasma lipoproteins. In intestinal cells, PC can be synthesized from dietary choline using the enzyme CTP:phosphocholine cytidylyltransferase alpha (CTα) to maintain cell integrity and homeostasis. Intestinal PC can also be obtained from dietary and biliary sources. Our lab has created an intestinal-specific CTα gene knockout mouse (iCTα−/−), with reduced de novo PC synthesis. Previous analysis has shown that high fat diet (HFD) fed iCTα−/− mice have decreased postprandial lipid secretion and weight gain. This data shows the importance of intestinal PC synthesis for proper lipid metabolism.

Hypotheses: My primary objective is to determine whether dietary lipid content affects lipid metabolism in CTα−/− mice, while my secondary objective is to determine whether appropriate lipid absorption can be restored with PC supplementation in iCTα−/− mice. My first hypothesis is that decreasing dietary lipids will in turn decrease fatty acid malabsorption in iCTα−/− mice. My second hypothesis is that PC supplementation will restore lipid absorption to appropriate levels in iCTα−/− mice.

Methods: In regards to dietary fat content and lipid absorption, control and iCTα−/− mice were fed a 4% (LFD) or 40% (HFD) fat/calorie diet. To determine whether PC supplementation aids in normalizing lipid absorption, control and iCTα−/− mice were fed a 4x choline (choline chloride) or 1x choline 3x PC (soy lecithin) 40% fat/calorie diet. Plasma and tissues were collected for analysis. Segments of the intestine (jejunum, ileum, and duodenum) were homogenized for lipid, protein, and gene expression. Gene expression was examined to elucidate changes in intestinal cell function in iCTα−/− mice.

Results: It was determined that weight gain and mRNA levels for genes involving lipid homeostasis in the jejunum were lowered in iCTα−/− mice fed the LFD and HFD, while jejunum PC and TG were significantly increased only in the HFD fed iCTα−/− mice. PC supplementation normalized jejunal PC levels in iCTα−/− mice, but did not result in improved lipid malabsorption.

Conclusion: Dietary lipid content appears to be responsible for some of the phenotype observed, but not all. More research is required to determine the complete effect of dietary lipids on intestinal homeostasis in iCTα−/− mice. Intestinal de novo PC synthesis is important for dietary lipid absorption. It appears that normal fat absorption requires PC through the de novo pathway, thus dietary PC cannot compensate for the loss of iCTα−/−.

Keywords: Phosphatidylcholine, lipid regulation, lipid malabsorption

ADI Research Day 2020
HOME-BASED RESISTANCE EXERCISE IMPROVES HEALTH RELATED QUALITY OF LIFE IN ADULTS WITH DIABETES AND CHRONIC KIDNEY DISEASE

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Background: Frailty can cause increased vulnerability to adverse health outcomes, such as falls, fractures, and reduced health-related quality of life (HRQoL). Frailty has been shown to be ameliorated by resistance exercise (RE). This open-labeled, randomized clinical trial examines the effect of a 6-month home based RE program on frailty outcomes.

Methods: Community dwelling adults with DM and CKD (54-83 years) ± frailty were randomized to either the intervention (n=14) or standard of care group (n=13) in a semi-block design (frail vs non-frail). Validated tools were used to assess a) frailty status (Rockwood Clinical Frailty Scale), b) muscle function (Short Physical Performance Battery [SPPB]), c) health related quality of life (HRQoL: SF-36 [body pain, social function, vitality, role emotional, physical composite scores, mental health composite scores]), d) Health Literacy (Functional, Communicative and Critical Health Literacy Index [FCCHL]), and e) activities of daily living (ADL; modified Barthel Index), pre- and post-intervention. Participants randomized into the intervention are led by video technology through a series of 5 resistance-band exercises 3 times weekly which target most major muscle groups. The exercise program is progressive, increasing volume gradually over the 6 months.

Results: Baseline mean (± SD) age (years), weight (kg), BMI (kg/m2) in the intervention and standard of care group were 67.2 ± 8.3, 66.5 ± 5.8, 95.5 ± 19.4 and 83.9 ± 15.7, 34.6 ± 6.1, 29.6 ± 3.7, respectively (p>0.05). Significant increases in HRQoL domains of bodily pain (61.5 ± 24.6 baseline vs 86.0 ± 20.0 6 months; p<0.05) and vitality (51.7 ± 19.2 baseline vs 87.5 ± 17.7 6 months; p<0.05) in frail patients only were observed in the intervention group. While % increases in the HRQoL domains of bodily pain (58% (frail) vs 38% non-frail; p <0.05) and vitality (39%frail vs 19% non-frail; p<0.05) were also observed the percentage increase in the non-frail participants were lower. No other significant changes in anthropometric, ADL scores, and muscle function were observed in frail/non-frail participants in either treatment arm.

Conclusions: These findings demonstrate that home-based exercise programming may positively influence some domains of HRQoL in community dwelling frail adults with DM and CKD.

Keywords: Diabetes, chronic kidney disease, resistance exercise, health-related quality of life

ADI Research Day 2020
COMPARISON OF CHEESE, YOGURT, AND MILK EFFECTS ON GLUCOSE HOMEOSTASIS IN MICE FED HIGH-FAT DIET

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**Background:** Many studies show an inverse or neutral association between dairy consumption and the risk of diabetes. Our lab’s previous work suggests that both low and high-fat cheese consumption improves glucose homeostasis in insulin-resistant (IR) rats. This study examined whether high-fat yogurt (YO) and milk (MI) have a similar effect as high-fat cheese (CH) on glucose homeostasis in IR mice.

**Methods:** An 8-weeks feeding intervention of a dairy diet (high-fat yogurt, milk, and cheese) was performed in high-fat diet-fed (HFD) insulin-resistant male C57Bl6/J mice (N=32 with n=8/group). A low-fat diet (LFD) control group was included (n=8). Mice were weighed weekly, and body fat mass was measured in week 6. One week before euthanasia, n=4 mice/group were administered an Insulin Tolerance Test (ITT) and n=4/group a Pyruvate Tolerance Test (PTT) to evaluate IR and hepatic glucose output capacity, respectively, following dairy consumption.

**Results:** Mice in the CH group weighed significantly more than LFD mice (p<0.01), but all mice on HFD had significantly more body fat %, independent of dairy consumption. There was no significant effect of diet on ITT, but the overall trend was similar to results seen in rats previously, i.e., dairy products improved insulin sensitivity in the HFD-fed IR mice. YO significantly increased hepatic glucose output in the PTT compared with LFD (p<0.05). The trial will be repeated to increase the n/group. Serum at the time of euthanasia will be used for metabolomics and lipid analysis. Liver tissue will be used to measure glucoregulatory enzymes and lipid content.

**Conclusion:** Preliminary results support our hypothesis that yogurt, milk, and cheese consumption improves insulin sensitivity in IR mice. Should this study find dairy beneficial for glucose regulation and identify potential mechanisms, research can be applied to humans.

**Keywords:** Dairy; Milk; Cheese; yogurt; insulin sensitivity; insulin resistant.
THE IMPACT OF DAPAGLIFLOZIN ON KETONE OXIDATION IN THE FAILING HEART

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Background: Over 600,000 people are living with heart failure (HF) in Canada. Sodium glucose co-transporter 2 inhibitors (SGLT2i), are a class of anti-diabetic drugs that prevent glucose re-absorption in the kidneys. They have been shown in clinical trials to decrease hospitalization and deaths in both diabetic and non-diabetic patients. However, the exact mechanism by which they are beneficial in heart failure has not been fully elucidated. There is a decrease in cardiac energy production in HF due to metabolic defects, and SGLT2i have been shown to increase circulating ketone body levels. Therefore, SGLT2i may be improving cardiac function in the failing heart through providing an extra source of fuel in the form of ketones. We therefore examined whether the beneficial effects of SGLT2i on HF outcomes are due to increased ketone oxidation.

Methods: 8 wk-old male C57BL6/N mice underwent sham or transverse aortic constriction (TAC) surgery to induce pressure overload HF over 3 weeks, following which they were treated with SGLT2i, dapagliflozin, or vehicle for 4 weeks. Blood samples were taken periodically to measure plasma levels of various metabolic substrates in fed and fasted states. Echocardiography was done at 3 and 6 weeks to assess cardiac function, and glucose tolerance tests were done. Hearts were subjected to isolated working heart perfusions at 7 weeks to measure energy metabolic rates. Immunoblotting was performed on heart, liver, and kidney tissue to assess expression of various proteins involved in major metabolic pathways.

Results: Preliminary immunoblots show up-regulation in the kidney of inflammasome marker NLRP3 and succinyl-CoA:3-ketoacid CoA transferase (SCOT), the rate limiting enzyme of ketone oxidation, in mice with HF that were treated with dapagliflozin. Key fatty acid and glucose oxidation enzyme levels were not significantly altered in the kidney or liver. Administration of dapagliflozin showed no effect on cardiac contractility and echocardiography parameters in preliminary data.

Conclusion: The increase in SCOT suggests a shift towards greater ketone utilization. Further experiments on how dapagliflozin directly impacts cardiac ketone oxidation and heart function in the failing heart are ongoing. A greater understanding of how SGLT2i improves HF outcomes will accelerate delivery of SGLT2i treatment for individuals with non-diabetic HF.

Key words: SGLT2i, heart failure, ketones, ketone oxidation, cardiac energy metabolism
SOCIO-DEMOGRAPHIC FACTORS ASSOCIATED WITH DIETARY SELF-CARE PRACTICE IN PEOPLE WITH TYPE-2 DIABETES: A LONGITUDINAL STUDY

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Background: Management of diabetes depends on adequate diabetes education and choice of a healthy lifestyle, including proper nutrition therapy. This study aims to investigate the longitudinal relationship between dietary self-care behaviors and socio-demographic factors in adults with type 2 diabetes.

Method: The Alberta’s Caring for Diabetes (ABCD) cohort is a longitudinal cohort of adults with type 2 diabetes established in 2011, which surveyed participants over 5 waves, with the last wave being in 2019. For these analyses, only responses from those who completed all 5 waves were included (N=488). Dietary self-care practice was measured by previously validated Summary of Diabetes Self-Care Activities (SDSCA) scale, which asks respondents to indicate how frequently they follow dietary recommendations (i.e., 0-3 days, 4-5 days, or 6-7 days per week). Multivariate multinomial logistic regression analyses were conducted to measure associations between socio-demographic factors (age, marital status, smoking status, income, education, diabetes duration) and dietary self-care practice.

Results: At baseline, the average age was 63.4 (SD 9.42) years, with the diabetes duration of 11.83 (SD 8.14) years. Just over half were male (55%), with college education or higher (56%), and most with an annual household income <$80,000 year (72%). The majority of respondents were Caucasian (95%), almost 73% were married and 50% were unemployed. These socio-demographic characteristics remained unchanged over the 5 waves. At baseline, older (over 65years) respondents were more likely to follow general diet recommendations for 6-7 days a week (RRR: 9.2, 95%CI: 1.57 to 54.51; p=0.01). Consistently over the five waves, females were more likely to follow either or both general and specific dietary recommendations for 4-5 days and 6-7 days a week in 2nd, 3rd and 4th wave. (Baseline, special diet, 4-5 days a week, RRR: 1.98, 95%CI: 1.18 to 3.31; p=0.009 and 6-7 days a week RRR: 2.57, 95%CI: 1.47 4.48; p=0.001). On the contrary, those who were not married were less likely to follow the general or special dietary recommendations for either 4-5 days or 6-7 days a week (Baseline, special diet, 4-5 days a week, RRR: 0.44, 95%CI: .25 to .78; p=0.005, and 6-7 days a week RRR: 0.59, 95%CI: .32 to 1.08; p=0.09,) over five waves.

Conclusion: Females were more likely to follow general and specific dietary recommendations and being not married was significantly associated with not following general and specific dietary recommendations throughout the study period. This study provides useful insight on how socio-demographic factors might influence the dietary healthcare behaviors in adults living diabetes.

Keywords: Type 2 diabetes, Socio-demographic status, SDSCA, Diet
Session 3
ASSOCIATION BETWEEN TYPE 2 DIABETES AND RISK OF PROSTATE CANCER: A SYSTEMATIC REVIEW OF OBSERVATIONAL STUDIES

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Background: Metabolic diseases such as type 2 diabetes (T2DM) may have a role in the development and progression of prostate cancer (PC); however, this association remains to be explored. The objective of this study was to investigate the evidence of an association between T2DM and risk of PC.

Methods: A systematic review was performed (MEDLINE, EMBASE and CINAHL) up to January 2020. Cohort, case-control, and cross-sectional studies that assessed the risk of PC associated with T2DM were included. The Newcastle-Ottawa Scale (NOS) was used to assess the quality of studies; those with NOS <7 or not published in English were excluded.

Results: The search yielded 321 studies and 23 studies were included. These were evaluated as all PC stages combined (n=20), early stages (stages I-II, n=8) and/or advanced stages (III-IV, n=12). Type 2 diabetes was associated with lower risk for PC in 55%, 50% and 41.7% of studies with all stages combined, early stages and advanced stages, respectively. Whereas T2DM was associated with a higher risk for PC in 5%, 0% and 16.6% of studies with all stages combined, early stages and advanced stages, respectively. In 46.2% of studies (n=6) a cumulative protective effect in individuals with prevalent T2DM for several years was observed (range: 3 months - ≥10y).

Conclusion: We found evidence that supports T2DM is protective of PC in all stages together and in the early stages but there is less evidence of the role of T2DM in the development of advanced PC. Mechanisms responsible for these different associations remains to be explored.

Keywords: Systematic review; Type 2 diabetes; Prostate cancer

ADI Research Day 2020
GLYCINE RECEPTOR SIGNALLING IN HUMAN PANCREATIC ISLETS

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Background: The pancreatic β cells secrete insulin, an essential hormone for glucose homeostasis. Insulin secretion is triggered by action potentials, and its main stimulus is glucose, but it can also be influenced by various neurotransmitters found in the pancreatic islets. Among them is glycine. This neurotransmitter acts through its ionotropic receptors (GlyRs), which are ligand-gated ion channels, permeable to the ion Cl-. Previous work from our group demonstrated that GlyRs are present in human β cells, and mediate glycine-evoked currents that contribute to cell depolarization, increasing insulin secretion. However, in islets from type 2 diabetic donors, GlyR signalling is impaired, and the mechanisms that lead to this change are still unknown. This work aims to investigate 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 cells from non-diabetic donors were cultured with 5.5 mM or 15 mM glucose for 2 days, while cells from type 2 diabetic donors were cultured in the control glucose concentration (5.5 mM). 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 µM glycine and 300 µM glycine with 10 µM strychnine (a GlyR antagonist). The identity of the cells was later confirmed by insulin immunostaining.

Results: The glycine current measured in β cells from type 2 diabetic donors (-4.185 pA/pF ± 3.447, n=8) and in cells that were cultured in 15 mM glucose for 2 days (-4.251 pA/pF ± 1.974, n=8) had smaller amplitude than those from cells cultured in control media (-11.09 pA/pF ± 2.648, n=21).

Conclusion: Glycine-evoked currents in β cells are diminished after 2 day culture with high glucose, to values similar to those found in cells from type 2 diabetic donors, showing that hyperglycemia is capable of modulating glycine receptor signalling.

Keywords: glycine receptors, hyperglycemia, human islets, type 2 diabetes, neurotransmitters

ADI Research Day 2020
ASSOCIATION BETWEEN DIETARY FATTY ACIDS CONSUMPTION AND CARDIOMETABOLIC RISK FACTORS IN INDIVIDUALS WITH OR WITHOUT INSULIN RESISTANCE: PRELIMINARY ANALYSIS OF THE NUTRITION AND IMMUNITY (NUTRIMM) STUDY

Jenneffer Rayane Braga Tibaes, Maria Ines Barreto Silva, Alexander Makarowski, Anna Thomsen, Paulina Blanco, Donna Vine, Sue Tsai, Caroline Richard

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Background: Dietary fats are associated with cardiovascular disease (CVD), and a shift from saturated to unsaturated fats is often recommended to reduce the risk of CVD. However, the effect of specific dietary fatty acids (FA) on CVD risk factor in the context of a standardized isocaloric North American diet remains unknown. This study aimed to investigate the association between dietary FA intake and cardiometabolic risk factors in individuals with or without insulin resistance (IR) in the context of an isocaloric North American diet.

Methods: Three groups of adults (Lean-normoglycemic (lean-NG; n=4), Obese-NG (n=7) and Obese-IR; n=6) consumed an isocaloric North American diet containing 35% fat (12.5% saturated fat), 48% carbohydrate (mainly refined), and 17% protein for 4 weeks. All meals were provided to participants. Blood samples were collected in the fasting state before and after the dietary intervention and cardiometabolic risk factors were measured. Changes in dietary intake (delta pre-post) were assessed using a food frequency questionnaire (FFQ) and intervention diet. In a subset of participants (n=6), FA composition in red blood cells (RBC) was analyzed by gas chromatography to confirm changes in dietary FA intake. Partial correlations analysis adjusted by group was performed to assess the association between changes in dietary intake and FA composition in RBC and changes in the lipid profile.

Results: The reduction in polyunsaturated FA (PUFA) intake during the intervention was associated with an increase in plasma non-high-density lipoprotein cholesterol (HDL-C) concentration (r= -0.542; p=0.04). Regarding omega-3, significant correlations were observed between docosahexaenoic acid (DHA; 22:6 n-3) and total cholesterol (TC) (r= -0.610), LDL-C (r=-0.704), and non-HDL-C (r= -0.632), between alpha-linolenic acid (18:3 n-3) and LDL-C (r= -0.694) and non-HDL-C (r = -0.676), and between eicosapentaenoic acid (EPA; 20:5 n-3) and LDL-C (r= -0.596; all p<0.05). The proportion of DHA was significantly lower in RBC after the intervention (1.5±0.57 vs. 0.99±0.52; p= 0.04), while we were underpowered to detect significant changes in the other omega-3 FA. Increase in cholesterol consumption was correlated with higher proportion of 14:0 (r=+0.998) and 17:0 (r=+0.959), and a decreased proportion of 18:1 n-9 (oleic acid; r=-0.978) in RBC.

Conclusion: The decrease in PUFA consumption, especially omega-3, after consuming a North American diet is associated with an increase in plasma cholesterol levels.

Keywords: obesity, fatty acids, cardiometabolic risk, North American diet.
EGG WHITE DERIVED BIOACTIVE PEPTIDE IRW IMPROVES GLUCOSE TOLERANCE AND INSULIN SIGNALING IN HIGH FAT DIET FED MICE

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Background: Food derived bioactive peptides have shown beneficial effects against cardiovascular diseases, obesity, and diabetes. Egg is broadly consumed and a great source of bioactive peptides. IRW is an egg ovotransferrin-derived ACE inhibitory tripeptide which has shown beneficial effects in reducing blood pressure in rodents and improving angiotensin II or TNF-α induced insulin resistance (IR) in vitro. Here, we hypothesize that IRW supplementation improves glucose tolerance and insulin sensitivity in skeletal muscle, by improving muscular insulin signaling and enhancing glucose transporter 4 (GLUT4) translocation to the plasma membrane. In addition, we hypothesize that IRW promotes fat mass reduction in high fat diet (HFD) induced obese mice.

Methods: C57BL/6 mice were fed HFD for 6 weeks, after that IRW was incorporated in their diet (45mg/kg body weight (IRW45) and 15mg/kg body weight (IRW15)) for another 8 weeks. The trial lasted 14 weeks with ad libitum access to food and water. Prior to euthanasia, insulin (2 IU/kg BW) was injected intraperitoneally to stimulate insulin signaling. Glucose tolerance and insulin sensitivity were measured by oral glucose tolerance test (OGTT) and insulin tolerance test (ITT), respectively. AKT phosphorylation and Glucose transporter 4 (GLUT4) were measured by western blot. Plasma insulin was measured by ELISA assay.

Results: IRW supplementation in a high dose improved OGTT and fasting glucose concentration (after 5 weeks of peptide feeding) compared to HFD, despite no improvements in ITT. Fasting insulin concentration and HOMA-IR were reduced by IRW 45 supplementation at the end of the trial. This was accompanied by reduced final body weight, final fat mass and fat mass gain. Moreover, % lean mass was higher in IRW45 supplemented animals than in the HFD group. In skeletal muscle, high dose of IRW enhanced insulin signaling (AKT phosphorylation) and GLUT4 amount in the cellular membrane.

Conclusion: IRW has potential to, in a high dose, reduced body weight, weight gain and fat mass gain. These effects were accompanied by improvement in glucose tolerance in vivo, decreased plasma fasting glucose, plasma insulin and HOMA-IR. At tissue level, in skeletal muscle, IRW enhanced AKT phosphorylation and GLUT4 translocation to the membrane; suggesting enhanced glucose uptake and improved insulin signaling.

Key words: Bioactive peptides, IRW, insulin resistance, prediabetes

ADI Research Day 2020
HYPOTHALAMIC GLUCOCORTICOID ACTION INDUCES CHANGES IN LIVER GENE AND PROTEIN EXPRESSION AFFECTING LIPID SECRETION

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**Background:** Impaired lipid homeostasis is a feature of diabetes and obesity. These metabolic diseases are associated with excessive levels and/or actions of GCs, which may contribute to dyslipidemia including elevated VLDL-TG secretion. The dysregulation of VLDL-TG secretion, particularly in metabolic disease states, remains largely unknown. Previously, we reported that direct glucocorticoid (GC) infusion into the mediobasal hypothalamus (MBH), a nutrient- and hormone-sensing region of the brain, stimulates triglyceride (TG)-rich very low-density lipoprotein (VLDL-TG) secretion. MBH GC action is mediated by its receptor (GR) as both acute and chronic inhibition of GRs specifically in the MBH negates the MBH GC-induced increase in VLDL-TG secretion. Furthermore, MBH GR loss-of-function lowers VLDL-TG secretion in high-fat diet (HFD)-induced hyperlipidemic rats, independent of changes in body weight. Presently, we aim to identify mechanisms that may underlie hypothalamic GC action on hepatic TG secretion in health and diet-induced hyperlipidemia.

**Methods:** Plasma TG levels and the rate of VLDL-TG secretion were measured following intravenous poloxamer injection with concomitant MBH infusions in 10h-fasted, conscious, freely moving Sprague Dawley rats implanted with MBH and vascular cannulae.

**Results:** Direct MBH GC infusion increased VLDL-TG secretion compared to MBH vehicle-infused controls, independent of changes in plasma apoB48, apoB100, FFAs, glucose, and corticosterone. Interestingly, the MBH GC-induced increase of VLDL-TG was associated with decreased hepatic Cpt1a and Ppara mRNA expression compared to controls. Pharmacological inhibition of MBH GRs normalized the MBH GC-induced increase of VLDL-TG and blocked the decrease in hepatic Cpt1a and Ppara mRNA expression, suggesting that MBH GC action may regulate hepatic FA oxidation. When VLDL-TG was increased by MBH GCs, no changes in hepatic expression of Dgat1/2, Fasn, or Lipin2 or protein levels of MTP, P-ACC/ACC, or FAS were observed compared to controls. In HFD-fed rats, basal plasma GCs, apoB48 and apoB100, as well as hepatic TG and Dgat2 expression, were increased.

**Conclusion:** Here, we provide preliminary evidence that hypothalamic GC action alters hepatic FA oxidation gene expression, which may contribute to the stimulatory action of hypothalamic GCs on hepatic lipid secretion in vivo. This data may provide insight on the aberrant liver lipid metabolism observed in diabetes and obesity and implicates a role of hypothalamic GCs.

**Keywords:** Glucocorticoids, VLDL-TG, Hypothalamus, Liver
Session 4
ESTABLISHING OR EXAGGERATING CAUSALITY FOR THE GUT MICROBIOME: LESSONS FROM HUMAN MICROBIOTA-ASSOCIATED RODENTS

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Background: Human diseases are increasingly linked with an altered or 'dysbiotic' gut microbiota, but whether such changes are causal, consequential, or bystanders to disease is, for the most part, unresolved. Human microbiota-associated (HMA) rodents have become a cornerstone of microbiome science for addressing causal relationships between altered microbiomes and host pathology.

Methods: A systematic literature review was conducted in June 2019 (with an updated literature search in October 2019) to assess the success rate of HMA murine models in establishing or implying a causal relationship between dysbiotic human microbiomes and disease or physiological conditions. Only studies that compared pathophysiological phenotypes in animals (germ-free or antibiotic treated) that received donor fecal samples from human individuals affected by a pathology versus healthy controls were included.

Results: We found that 95% of published studies (36/38) on HMA rodents reported a successful transfer of pathological phenotypes to recipient animals, and many extrapolated the findings to make causal inferences to human diseases. Only 63% of the studies (24/38) tested for dysbiosis in the original human donor samples, and only 29% (11/38) confirmed that at least some aspect of the human donor dysbiosis was replicated in the recipient animals. Only 34% of the studies (13/38) identified potential underlying mechanisms linking the dysbiotic microbiome with disease. Finally, 84% of the included studies (32/38) conducted pseudoreplication by artificially inflating the number of replicates in the rodents compared to the number of human donor samples.

Conclusion: We argue that the exceedingly high rate of inter-species transferable pathologies is likely implausible and overstates the role of the gut microbiome in human disease. We advocate for a more rigorous and critical approach for inferring causality to avoid false concepts and prevent unrealistic expectations that may undermine the credibility of microbiome science and delay its translation.

Keywords: human microbiota-associated rodents, dysbiosis, chronic disease, causality

ADI Research Day 2020
COMBINATION OF AN ALGINATE-BASED ISLET ENCAPSULATION DEVICE WITH A PREVASCULARIZATION STRATEGY TO ENABLE IMMUNOSUPPRESSION-FREE SUBCUTANEOUS ISLET TRANSPLANTATION

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Background: Islet transplantation (IT) is an effective therapy for patients with type 1 diabetes (T1D), however, the need for lifelong immunosuppression is a major limitation. Islet encapsulation could solve this issue. Its clinical translation requires that implantation sites, such as the subcutaneous space (SC), be optimized for efficient engraftment and function. Our device-less (DL) approach harnesses the foreign body response to promote prevascularization of the SC and enables long-term diabetes reversal in this hostile environment. However, it is not immune protecting. Conversely, the recently-developed thread-reinforced alginate fiber for islet encapsulation (TRAFFIC) device allows 100% long-term diabetes reversal without immunosuppression in allogeneic models of IT. However, it has only been tested in the intraperitoneal (IP) cavity, which complicates safe and effective clinical translation. We hypothesize that our DL + TRAFFIC approach will allow islet engraftment in the SC and immunosuppression-free long-term diabetes reversal.

Methods: C57BL/6 recipient mice will have nylon catheters implanted into the SC of the abdomen 6 weeks before IT to allow prevascularization at the site. One the day of transplantation, we will manufacture and implant TRAFFIC devices with 500 IEQ (BALB/c donor islets) into the DL site. Controls include: TRAFFIC + IP, TRAFFIC + direct subcutaneous (no DL prevascularization), and kidney capsule (no encapsulation, islet quality control). Glucose monitoring thrice a week will be performed for 180 days. Immunohistochemistry of the graft will be done at endpoint.

Results: the TRAFFIC device protects islets implanted in the SC from alloimmunity and has no impact on islet survival, with mouse islets maintaining their architecture after prolonged periods of implantation. More importantly, we have achieved long-term diabetes reversal in our stringent model of allogeneic IT using our TRAFFIC + DL approach, with mice maintaining normoglycemia for nearly 6 months without any immunosuppression. In contrast, TRAFFIC devices implanted directly in the subcutaneous space did not correct hyperglycemia; islet implanted under the kidney capsule quickly reversed hyperglycemia, but were rejected within 21 days, as expected. Glycemic control with our TRAFFIC + DL approach is comparable to TRAFFIC + IP controls.

Conclusions: the TRAFFIC + DL approach supports long-term immunosuppression free diabetes reversal and glycemic control that is comparable to TRAFFICs implanted in the IP cavity. These findings are extremely promising due to its potential for clinical translation. We are currently extending our experience with xenogeneic models including neonatal pig islets and human islets to assess the potency and efficacy of our combined approach.
SUMOylation is a post-translational conjugation (PTM) of small ubiquitin-like modifier (SUMO) peptides to target lysine residues. With increasing oxidative stress induced by streptomycin (STZ), SUMOylation exerts a protective effect on β-cell mass at the expense of insulin secretion. It remains unknown how SUMOylation regulates β-cell viability and function in response to metabolic stress such as a high fat diet (HFD), where β-cell functional and mass are known to be upregulated in mice. To investigate the role of SUMOylation in pancreatic β-cells in this context, we initially put mice with a pancreas-specific loss of the sentrin-specific protease 1 (SENP1), generated by crossing the Pdx-Cre line with SENP1fl/fl mice (pSENP1-KO), on HFD. Male pSENP1-KO mice became much more glucose intolerant following 8-weeks HFD than pSENP1-WT littermates, and this was more significant in response to oral than intraperitoneal (IP) glucose. This phenotype was less obvious in female mice and was accompanied by impaired glucose- and incretin-stimulated insulin secretion in vitro and decreased islet mass. However, this might be due to unspecific knockout of SENP1 in the gut and in the islets owing to the Pdx-Cre used. Therefore, we generated β-cell -specific SENP1 knockout mice by crossing the INS1-Cre knock-in mouse line with the SENP1fl/fl mice (βSENP1-KO). βSENP1-KO mice showed impaired oral glucose after HFD associated with decreased insulin secretion in response to glucose and incretin without change in β-cell mass. Thus, SENP1 is important for β-cell function following HFD without affecting compensatory increase in β-cell mass.
LAYER BY LAYER COATING PRESERVES HUMAN AND MOUSE ISLETS IN VITRO AND IN VIVO FUNCTIONAL POTENCY

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Background: Pancreatic islet transplantation represents a proven therapeutic strategy to restore physiologic glycemic control for patients with T1DM who suffer from life-threatening severe hypoglycemia unawareness. However, several limiting factors prevent islet transplantation from replacing exogenous insulin therapy, including organ donor shortage and lifelong immunosuppression. Islet encapsulation strategies have the potential to reduce the adaptive immune response. We hypothesize that conformal islet coating with poly(N-vinylpyrrolidone) (PVPON) and tannic acid (TA) PVPON/TA will increase the engraftment efficacy of human islet xenografts as well as murine islet allografts.

Methods: Conformal coating of human and murine pancreatic islets was performed by utilizing non-toxic, non-ionic and biocompatible PVPON and TA, to form 3.5 bilayer deposits. Confirmation that PVPON/TA does not hinder islet function was examined by the in vitro function of coated and non-coated human islets. In vitro viability assays included static glucose stimulated insulin secretion, oxygen consumption rates and membrane integrity. In vivo function was assessed by transplanting these human islets (1500IEQ) into diabetic immunodeficient Rag-/- mice. Subsequently, the immunoprotective properties of PVPON/TA coating were examined by transplanting coated and non-coated islets in our well-established murine islet allograft model. BALB/c (H2d) mice were served as islet donors while STZ-induced diabetic C57BL/6 (H2b) mice served as islet recipients.

Results: Both control and coated islets exhibited similar results in all in vitro assays performed (P>0.05). Human islets recipients transplanted with PVPON/TA coated islets reversed diabetes (n=4), proving this coating technique is non-toxic. Interim, data from allograft recipients demonstrates that PVPON/TA coating as a monotherapy as well as adjuvant to systemic immunosuppression reduces intragraft inflammation and delays allograft rejection.

Conclusions: The present study demonstrates that PVPON/TA coated islets retain their in vitro and in vivo functional potency. This transplant approach has the potential to decrease post-transplant inflammatory responses, high possibility of translation to clinical investigation, improve islet allograft survival and reduce the need for systemic immunosuppression.

Key words: Islets transplantation, Encapsulation, Immune protection.

ADI Research Day 2020
**ESCHERICHIA COLI IS REQUIRED FOR ADVERSE METABOLIC OUTCOMES ASSOCIATED WITH EARLY LIFE AMOXICILLIN EXPOSURE IN MICE**

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**Introduction**
The postnatal period is a critical window for β-cell function and growth due to adaptive responses to metabolic changes and stressors. We have shown that early life amoxicillin treatment alters pancreatic development and results in impaired glucose tolerance later in life and have associated these changes with a bloom of *Escherichia coli*.

**Methods**
To test the causal role of *E. coli* in this phenotype, C57BL6/J *E. coli*-free mouse breeding pairs were randomly assigned to one of the following groups: no treatment control (C), control plus amoxicillin (CA), *E. coli* colonization (E), or *E. coli* colonization treated with amoxicillin (EA). Half of the animals from each litter were terminated at postnatal day 14 while the other half were weaned and switched to a 45 kcal% high-fat diet at 3 weeks of age. Insulin and glucose tolerance tests were carried out in 10-weekold mice.

**Results**
Fasting blood glucose and fasting blood insulin in EA mice was significantly higher than C, E and CA mice (p< 0.01). Mice from EA (p<0.001) and E (p<0.05) had impaired glucose tolerance compared with C and CA as indicated by higher area under the curve (AUC) values. There were no differences detected in insulin tolerance.

**Conclusion**
Exposure to *E. coli* with or without amoxicillin caused reduced glucose tolerance. Amoxicillin caused a further deterioration of fasting blood glucose. The results of this study suggest that *E. coli* plays an important role in altered metabolic development in neonatal mice, with effects on metabolic health being exaggerated by antibiotic treatment.

**Keywords**
Diabetes, postnatal life, pancreatic β-cell function, gut microbiota

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