2017 RESEARCH DAY
08.30–16.30 | Lister Centre, Maple Leaf Room | University of Alberta
THURSDAY OCTOBER 5

KEYNOTE SPEAKER
MEGAN LEVINGS, PhD
Professor, Department of Surgery, University of British Columbia
Head, Childhood Diseases Theme,
BC Children’s Hospital Research Institute, Canada
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Thank you to our generous event sponsors MERCK and Eli Lilly and to the Alberta Diabetes Foundation for providing door prizes.

Leading the World in the Prevention, Treatment and Cure of Diabetes
Welcome to the 2017 Alberta Diabetes Institute Research Day. Activities at the ADI range from the study of immunology, basic cell/molecular biology and bioengineering to clinical research, nutrition and exercise, population health and the development of public policy in diabetes care. We also continue to grow – we now have 65 principal investigators and 200 trainees/staff, making us one of the largest and most active diabetes centres worldwide. A testament to our growth is the use of the Lister Centre for the second year in a row for our Research Day, as we have outgrown the ADI in just a few short years.

This annual event is intended to provide a forum to showcase the research efforts of our ADI trainees – this year our trainees will present 8 full oral presentations, 12 mini oral presentations, and 30 poster presentations. We have added more mini-talks so that more of you get the chance to present your research orally. For some of our trainees it will be the first time presenting their research in front of an audience of their peers, supervisors and principal investigators. Today is about giving you, as the next generation of diabetes researchers, an opportunity to present your most recent exciting results and ideas.

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 endeavours and I encourage you to ask questions during both the talks and poster sessions. Enjoy the day and watch out for our 10th Anniversary celebrations on November 14th that include a social event and the chance to see the High Level Bridge lit up in our colours of blue and green!

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. Finally, I would also like to take this opportunity to thank our sponsors Merck Canada and Eli Lilly Canada for their generous and continued support of this research day and for sponsoring the visit of our esteemed guest speaker, Dr. Megan Levings.

Best Regards,

Peter Light, PhD
Director, Alberta Diabetes Institute
Dr. Charles A. Allard Chair in Diabetes Research
Professor of Pharmacology
# 2017 ADI RESEARCH DAY

**Thursday October 5**  
LISTER CENTRE, Maple Leaf Room, University of Alberta

## MORNING SESSION

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| 0845-0945 | Keynote Speaker | Dr Megan Levings  
**Head, Childhood Diseases Theme, BC Children’s Hospital Research Institute, Canada**  
**REGULATORY T CELLS IN DIABETES: BIOMARKERS, ANTIGEN SPECIFICITY, AND CLINICAL TRIALS** |
| 0946-1001 |  
**SESSION 1**  
**Chair – Rene JACOBS** | Meghan INGSTRUP  
**Supervisor: J Johnson**  
**RAPPORT ESSENTIAL TO PROVIDE EFFECTIVE SOCIAL SUPPORT FOR WOMEN WHO HAVE HAD A GESTATIONAL DIABETES PREGNANCY ADHERE TO AN ACTIVE LIVING BEHAVIOR INTERVENTION** |
| 1002-1017 |  
**SESSION 1**  
**Chair – Rene JACOBS** | Esmé DIJKE  
**Supervisor: West**  
**EXPANSION OF REGULATORY T CELLS (TREGS) ISOLATED FROM DISCARDED HUMAN THYMUS WITH GOOD-MANUFACTURING-PRACTICE (GMP)-COMPATIBLE TETRAMERIC ANTIBODY COMPLEXES** |
| 1018-1025 |  
**SESSION 1**  
**Chair – Rene JACOBS** | Nicole BROCKMAN  
**Supervisor: Yardley**  
**Mini talk: RESISTANCE EXERCISE IN TYPE 1 DIABETES: SEX-RELATED DIFFERENCES** |
| 1026-1033 |  
**SESSION 1**  
**Chair – Rene JACOBS** | Kim HO  
**Supervisor: Lopaschuk**  
**Mini talk: THE SGLT2 INHIBITOR EMPAGLIFLOZIN IMPROVES CARDIAC FUNCTION IN DB/DB MICE WITHOUT STIMULATING KETONE OXIDATION** |
| 1034-1041 |  
**SESSION 1**  
**Chair – Rene JACOBS** | Scott CAMPBELL  
**Supervisor: Light**  
**Mini talk: THE DPP4 INHIBITOR SITAGLIPTIN INCREASES INTRA-ISLET ACTIVE GLP-1 LEVELS IN HUMAN ISLETS AND MAY CONFER ADDITIONAL PROTECTION FROM CELL DEATH** |
| 1042-1052 | BREAK | PRAIRIE ROOM |
| 1053-1107 |  
**SESSION 2**  
**Chair – Jane YARDLEY** | Bassem SALAMA  
**Supervisor: Korbutt**  
**ENHANCING SUBCUTANEOUS ISLET GRAFT VIABILITY AND FUNCTION USING FIBRIN** |
| 1108-1123 |  
**SESSION 2**  
**Chair – Jane YARDLEY** | Derek TOMS  
**Supervisor: Ungrin**  
**MULTIFACTORIAL OPTIMIZATION OF PSEUDOSLET PRODUCTION** |
| 1124-1131 |  
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**Chair – Jane YARDLEY** | Katarina ONDRUSOVA  
**Supervisor: Light**  
**Mini talk: SUBCUTANEOUS WHITE ADIPOCYTE BIOLOGY IS AFFECTED BY BLUE LIGHT VIA MELANOPSIN/TRPC CHANNEL ACTIVATION** |
| 1132-1139 |  
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**Chair – Jane YARDLEY** | Lauren CORMIER  
**Supervisor: J Johnson**  
**Mini talk: DIETARY INTAKE OF WOMEN IN THE HEALTHY EATING AND ACTIVE LIVING AFTER GESTATIONAL DIABETES MELLITUS TRIAL (HEALD-GDM)** |
| 1140-1147 |  
**SESSION 2**  
**Chair – Jane YARDLEY** | Amanda LIU  
**Supervisor: Mager**  
**Mini talk: DIETARY INTAKE AND MICRONUTRIENT SUPPLEMENTATION IN YOUTH WITH CELIAC DISEASE (CD) WITH AND WITHOUT TYPE 1 DIABETES (T1D)** |
| 1148-1230 | LUNCH | PRAIRIE ROOM |
## POSTER PRESENTATIONS

1230-1355  Posters located at the back of Maple Leaf Room

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KEYNOTE SPEAKER

Megan Levings, PhD

Professor, Department of Surgery,
University of British Columbia

Head, Childhood Diseases Theme,
BC Children’s Hospital Research Institute

Dr. Megan Levings has been in the UBC Department of Surgery since 2003 when she was recruited back to Canada as a Canada Research Chair in Transplantation. In 2011 she joined the BC Children’s Hospital Research Institute where she now heads the Childhood Diseases Theme. Dr. Levings’ scientific career started with summer research positions in a fruit fly genetics lab at Simon Fraser University. She then did her graduate training in the genetics program with Dr. John Schrader at UBC. In 1999 she joined Dr. Maria Grazia Roncarolo’s lab in Milan, Italy, undertaking postdoctoral training in the emerging area of immune regulation. She was among the first groups to show that a special kind of white blood cell, known as a T regulatory cell, could be used as a therapy to stop harmful immune responses. She continues this line of research at UBC, and is now internationally recognized in the field of human immunology and chairs the Federation of Clinical Immunology Societies Centres of Excellence. She leads a vibrant group of trainees and staff who are researching how to use T regulatory cells to replace conventional immunosuppression in the context of transplantation and autoimmunity.
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PRIZES

Prize announcements at 4:20-4:30 pm

ORAL PRESENTATION AWARDS

Mini Oral Presentation
12 entries
- 1 Best Award “basic research”
- 1 Best Award “clinical/population health research”

Full Oral Presentation
8 entries
- 1 Best Award “basic research”
- 1 Best Award “clinical/population health research”

POSTER PRESENTATION AWARDS

Junior Posters (Summer Students)
7 entries
- 1 Best Award

Junior Posters (MSc Students)
6 entries
- 1 Best Award

Senior Posters (PhD Students)
11 entries
- 2 Best Award

Senior Posters (Postdocs, Research Associates, Technicians)
6 entries
- 1 Best Award

TRAINEE CHOICE AWARD
- 1 Trainee Choice Award (only trainees vote – fill in ballot, their choice of best oral presentation)

DOOR PRIZES
- Door prize name draws at end of ADI Research Day, must be in attendance to collect a prize!
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**2017 ADI RESEARCH DAY**  
Thursday October 5  
LISTER CENTRE, Maple Leaf Room, University of Alberta

**ABSTRACTS**

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RAPPORTE ESSENTIAL TO PROVIDE EFFECTIVE SOCIAL SUPPORT FOR WOMEN WHO HAVE HAD A GESTATIONAL DIABETES PREGNANCY ADHERE TO AN ACTIVE LIVING BEHAVIOR INTERVENTION

Meghan Ingstrup¹, Lisa A Wozniak¹, Nonsikelelo Mathe¹, Abdulrhman Alghamdi¹, Lauren Cormier¹, Sonia Butalia², Margie H Davenport³, Jeffrey A Johnson¹, Steven T Johnson¹,4.

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Background: We implemented a healthy eating and active living intervention with women with a previous Gestational Diabetes Mellitus (GDM) pregnancy. The intervention was based on the Healthy Eating and Active Living for Diabetes program (HEALD), an effective 24-week walking program for people with type-2 diabetes led by an exercise specialist. In the current intervention, peer counselors with a previous GDM pregnancy were trained to support behavior change, and encouraged healthy eating and active physical activity among women via weekly telephone calls. The objective of this study was to understand the usefulness of social support, including peer counseling, to promote behavior change among women with a previous GDM pregnancy.

Methods: We used a qualitative descriptive approach. We purposefully sampled women who completed the intervention and the peer counselors who provided weekly support and invited them to participate in semi-structured interviews. Data were analyzed using content analysis until saturation was reached.

Results: In total, nine women and two peer counselors participated. Participants explained that social support helped promote behavior change when rapport was present. When rapport was developed peer counselors were reported as motivational, were better able to help identify barriers to participation, and the women were more receptive to these suggestions. Some participants did not receive the support they needed from their counselor. They relied on social support (e.g., emotional support, engaging in physical activity with the women, or providing childcare while women walked) from partners, friends, and peers with whom rapport was already established.

Conclusions: Overall, social support, including peer counseling, promoted behavior change when a relationship was established and the participants' needs were met. This research will inform future implementation of effective social support interventions among women with previous GDM.

Key words: Gestational Diabetes Mellitus, Social Support, Behavior Change.

ADI Research Day, October 5, 2017
EXPANSION OF REGULATORY T CELLS (TREGS) ISOLATED FROM DISCARDED HUMAN THYMUS WITH GOOD-MANUFACTURING-PRACTICE (GMP)-COMPATIBLE TETRAMERIC ANTIBODY COMPLEXES

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Background: Tregs are a promising therapeutic tool in organ transplantation and autoimmunity to suppress destructive immune responses. Challenges include isolation of pure Tregs and expansion to clinically relevant numbers while maintaining stable function. We previously showed that abundant CD25+ thymocytes can be isolated from discarded human thymuses, routinely removed during pediatric cardiac surgery, and expanded to highly suppressive and stable Tregs using artificial antigen-presenting cells (APCs). For transition into GMP setting, we studied whether thymic Tregs (tTregs) can be expanded using GMP-compatible non-APC-based tetrameric antibody complexes.

Methods: Thymocytes were isolated by mechanical dissociation from thymuses obtained during pediatric cardiac surgery. CD25+ tTregs were isolated by magnetic-bead cell separation and expanded in the presence of IL-2 and rapamycin with anti-CD3/CD28 antibody complexes, anti-CD3/CD28/CD2 antibody complexes or artificial anti-CD3-loaded APCs. Treg expansion was assessed by analyzing expansion rate, viability, FOXP3 expression and suppressive capacity of the proliferation of anti-CD3/28-stimulated T cells.

Results: tTregs cultured with anti-CD3/CD28/CD2 antibody complexes had a higher expansion rate than those cultured without anti-CD2 (mean±SEM fold expansion at day 14: 46 ±31 vs. 29±19, respectively). Although their expansion rate was lower compared to tTregs cultured with APCs at day 11, it was comparable on day 14. Viability at day 14 was >80% for all culture conditions. The vast majority of tTregs cultured with antibody complexes maintained high FOXP3 expression (mean±SEM % FOXP3+ cells: anti-CD3/CD28: 83±5% and anti-CD3/CD28/CD2: 85±4%), comparable to APC-cultured tTregs. tTregs cultured with antibody complexes potently suppressed proliferation of anti-CD3/CD28-stimulated T cells with >70% inhibition at a Treg:responder cell ratio of 1:2.5.

Conclusion: Thymic Tregs can be expanded with tetrameric antibody complexes and maintain high FOXP3 expression and potent suppressive capacity. By using non-APC-based tetrameric antibody complexes, we will be able to transition into a GMP setting for further optimization of an expansion protocol for therapeutic tTregs.

Keywords: Regulatory T cells, cell therapy, GMP, cell expansion
RESISTANCE EXERCISE IN TYPE 1 DIABETES: SEX-RELATED DIFFERENCES

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**Background:** Resistance exercise (RE) is extremely beneficial for individuals with type 1 diabetes (T1D). While there are known sex-related differences in physiological responses to RE in nondiabetic individuals, no research exists on sex-related differences in blood glucose (BG) responses to RE in T1D individuals. These differences could have important implications for preventing hypoglycemia during and after exercise. This study aimed to determine if sex-related differences exist in BG responses to RE in individuals with T1D.

**Methods:** A secondary data analysis was conducted on pooled data from two studies with identical RE protocols for individuals with T1D. The analysis included physically active T1D adults [sex: male n=13 and female n=10; age: 34 ± 15 and 29 ± 8 (P= 0.33); height: 1.79 ± 0.05 and 1.68 ± 0.05 m (P < 0.001); weight: 84 ± 11 and 71 ± 12 kg (P= 0.02); BMI 26 ± 3 and 25 ± 4 (P= 0.56); predicted VO2max: 51 ± 10 and 40 ± 8 ml/kg/min (P=0.01); HbA1C: 7.1 ± 1.0 and 7.3 ± 0.7 (P= 0.68); and diabetes duration: 15 ± 12 and 16 ± 7 yrs (P=0.88)]. The RE session, lasting approximately 45 minutes and consisting of seven resistance exercises (three sets at eight repetitions maximum), took place in the late afternoon. Plasma glucose samples were collected pre-, immediately post-, and one hour post-exercise. Interstitial glucose levels were recorded through continuous glucose monitoring 24 hours pre-, during and 24 hours post-exercise.

**Results:** There was a significant sex by time interaction (P < 0.001) in plasma glucose levels during exercise. Plasma glucose decreased significantly in males from 8.6 ± 0.7 to 6.3 ± 0.6 mmol/L (P < 0.001) during exercise, whereas females experienced no significant change (7.2 ± 0.4 to 7.3 ± 0.4 mmol/L, P= 0.999). In the 6 hours following exercise, males experienced significantly more hypoglycemia with respect to area under the curve (< 3.9 mmol/L) than females (P=0.048).

**Conclusion:** Males may have a greater risk of hypoglycemia with an acute bout of RE than females. Further research is needed to examine this phenomenon more closely.

**Keywords:** type 1 diabetes, sex differences, resistance exercise

ADI Research Day, October 5, 2017
THE SGLT2 INHIBITOR EMPAGLIFLOZIN IMPROVES CARDIAC FUNCTION IN DB/DB MICE WITHOUT STIMULATING KETONE OXIDATION

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Background: The antihyperglycemic effects of SGLT2 inhibitors, such as empagliflozin, have recently been shown to improve cardiovascular outcomes in diabetic patients. The mechanisms for cardioprotection are not clear but have been proposed to occur as a result of increased blood ketone levels. Ketones have been proposed to be a superfuel, which can increase the efficiency of cardiac metabolism in diabetic patients, although this has not yet been demonstrated. We therefore determined whether empagliflozin affects ketone oxidation and cardiac efficiency in the hearts of diabetic db/db mice.

Methods: db/db mice (18 weeks of age) were administered empagliflozin via the food at a dose of 10 mg/kg/day (db/db+emp) or were administered vehicle (db/db+veh) for a 4-week period. A third group of C57BL/6 mice was fed food with vehicle. Isolated working hearts were perfused with 0.8 mM palmitate, 5 mM glucose, 500 μM β-hydroxybutyrate (β-OHB), and 500 μU/mL insulin to measure fatty acid oxidation, glucose oxidation, β-OHB oxidation, glycolysis, O2 consumption, and cardiac efficiency (cardiac work/O2 consumption).

Results: db/db+veh mice had elevated fasting basal blood glucose levels, and this was significantly decreased in db/db+emp mice. Compared to C57BL/6, db/db mice had a decreased cardiac function and efficiency, which was associated with increased fatty acid oxidation, decreased glucose oxidation, and decreased β-OHB oxidation. Empagliflozin improved cardiac function, but did not affect cardiac efficiency, fatty acid oxidation, glucose oxidation, or β-OHB oxidation.

Conclusion: Empagliflozin treatment increases cardiac function, but this is not related to a stimulation of cardiac ketone oxidation.

Keywords: cardiac, metabolism, empagliflozin, diabetes, ketones
THE DPP4 INHIBITOR SITAGLIPTIN INCREASES INTRA-ISLET ACTIVE GLP-1 LEVELS IN HUMAN ISLETS AND MAY CONFER ADDITIONAL PROTECTION FROM CELL DEATH

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Background: Recent studies in genetic mouse models suggest that intra-islet GLP-1 is required for proper glucose homeostasis, highlighting the importance of paracrine GLP-1 signalling within the islet. However, information on intra-islet GLP-1 secretion and action within human islets is lacking. As alpha cells secrete GLP-1 and may also express DPP4, treatment with the DPP4 inhibitor sitagliptin should increase levels of active GLP-1 within the islet. Therefore, we determined if DPP4 is expressed within islets and studied the effects of sitagliptin on 1) active and total GLP-1 levels and 2) cell survival in human islets.

Methods: Human islets were cultured at 6.1 mmol/L glucose with or without sitagliptin (200 nmol/L). Active and total GLP-1 levels were measured using an immunoassay (MSD). Islet cell death was induced by serum withdrawal and culture time (48 hour) and detected with Sytox Green.

Results: Western blot analysis demonstrated that human islets express significant levels of DPP4. Furthermore, active GLP-1 levels were significantly increased by ~7-fold when islets were cultured with sitagliptin (P<0.05, N=3) and this positively correlated with increased islet cell survival.

Conclusions: Our results confirm that human islets are capable of secreting significant amounts of GLP-1 and that DPP4 inhibition elevates intra-islet active GLP-1. Furthermore, the elevation of active GLP-1 with sitagliptin positively correlated with increased islet cell survival, suggesting that DPP4 inhibition in human islets may confer additional protection from cell death.

Key words: DPP4, GLP-1, sitagliptin, human islet, cell survival

ADI Research Day, October 5, 2017
ENHANCING SUBCUTANEOUS ISLET GRAFT VIABILITY AND FUNCTION USING FIBRIN

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**Background:** Tight glycemic control is imperative to circumvent hyperglycemic complications type-1 diabetes (T1D) patients. Islet transplantation is an attractive alternative to exogenous insulin therapy, and median insulin independence rates acquired by islet infusion are comparable to whole pancreas transplantation. Extrahepatic sites are being investigated extensively to avoid the drawbacks of islet infusion into the portal venous tree. Subcutaneous space (SC) is a promising site, due to ease of graft transplantation, monitoring and graft retrieval. Yet, hypoxia remains a major impediment for long-term islet survival. Fibrin aids in amending tissue oxygenation through vascular remodeling and neovascularization. We investigated the capability of fibrin to improve graft survival and function in SC, as a potential ectopic site.

**Methods:** 5K neonatal porcine islets (NPI) were placed either alone under the kidney capsule (KC; n=4), or subcutaneously embedded in a fibrin scaffold (SC; n=7), in diabetic Rag-1 mice. Mice were monitored metabolically for reversal of hyperglycemia, and post-mortem graft assessment for viability and hormonal activity.

**Results:** All mice from the two experimental groups returned normoglycemic between 5 and 10 weeks post transplantation. During IPGTT, both cohort displayed rapid clearance of glucose within the first 60 minutes, and computed AUC revealed no significant difference between two groups. At experiment endpoint, KC cohort received survival nephrectomies, and returned diabetic within 48 hours after removing graft-bearing kidneys. Pancreases from SC transplants were analyzed for total cellular insulin content, and revealed near total ablation of recipients’ β-cells, confirming the effect graft function on reversing DM. Macroscopic observation of SC grafts showed noticeable increase in minute blood vessels at graft site. IHC staining for insulin-positive cells revealed robust staining, while immune fluorescence staining for insulin- and CD31-positive cells displayed newly formed capillaries, existed between and within matured NPI grafts.

**Conclusion:** NPI embedded in fibrin scaffolds and placed SC remained viable, and were able to reverse diabetes and maintain euglycemia in mice up to 21 weeks post transplantation. Results obtained from this newly investigated site are comparable to KC site, implying the capability of subcutaneous space as a potential ectopic transplant site.

**Keywords:** Type 1 DM - Islet xenotransplantation - Neonatal porcine islets - Subcutaneous space

ADI Research Day, October 5, 2017
MULTIFACTORIAL OPTIMIZATION OF PSEUDOISLET PRODUCTION

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BACKGROUND: While exogenous insulin delivery can palliate the effects of type 1 diabetes, cell-based therapies seeking to replace lost beta cells show promise in animal models and the clinic. Chief among these is the Edmonton protocol that makes use of islets from cadaveric donor pancreas. This procedure, however, is hampered by limited donor tissue as each recipient may need islets from as many as three donors. Research in this area has identified many factors that may improve islet function, yet variation between model systems and research strategies largely precludes a unified understanding necessary to reduce the number of donor islets needed per treatment.

METHODS: Making use of our novel microwell technology (AggreWell) for the ultra-high throughput generation of engineered cellular aggregates, we have begun developing a platform for optimizing bioprocessing protocols. We incorporate statistical design of experiments (DOE) methodology, a formalized process that maximizes the amount of information that can be gained from a limited number of experimental data points, to systematically optimize the production of engineered pseudoislets from human donor pancreas tissue.

RESULTS: We have previously shown that pseudoislets perform as well as native islets in reversing glucose intolerance in diabetic mouse models. To facilitate high throughput screening and eventual scale-up, we successfully produced both 96-well microwell microplates, and prototype microwell bioreactors capable of generating 50,000 aggregates in a single experimental run (compared to 200 per well of the 96-well microplate). We screened over thirty factors gleaned from the literature, to identify those that significantly affected pseudoislet glucose-stimulated insulin secretion (GSIS) either alone, or in combination, using DOE. With a reduced list of factors a more complex experimental design, currently underway, will be used to model the system and arrive at an optimized bioprocess wherein GSIS output can be maximized per input islet cell.

CONCLUSION: By systemically testing multiple factors to improve pseudoislet function, we aim to develop a unified dataset and ultimately reduce the quantity of donor tissue needed for islet transplantation. Furthermore, the formation of pseudoislets optimized using microwell technology can be scaled to any production level requirements. We provide a platform upon which any cell-based therapies for type 1 diabetes can be improved in an efficient and logical manner; with the ability for direct translation to in vivo testing.

KEYWORDS: design of experiments; pseudoislets; bioprocess optimization.

ADI Research Day, October 5, 2017
SUBCUTANEOUS WHITE ADIPOCYTE BIOLOGY IS AFFECTED BY BLUE LIGHT VIA MELANOPSIN/TRPC CHANNEL ACTIVATION

Katarina Ondrusova, Mohammad Fatehi, Amy Barr, Zofia Czarnecka, Wentong Long, Kunimasa Suzuki, Scott Campbell, Koenraad Philippaert, Matthew Hubert, Edward Tredget, Peter Kwan, Nicolas Touret, Martin Wabitsch, Kevin Y. Lee, Peter E. Light

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Background: Ambient light regulates various biological processes such as circadian rhythms, where blue light activates melanopsin (OPN4 gene), a Gq protein coupled photoreceptor, that opens TRPC channels in retinal ganglion cells. Given the large human skin surface area exposed to sunlight, light stimuli may directly affect underlying subcutaneous white adipose tissue. As indication of this, we have discovered the presence of a blue light (470 nm)-sensitive inward current in human and murine differentiated adipocytes, that is eliminated in the absence of light stimulation.

Methods: PCR was used to determine expression of OPN4 and TRPC channel variants in human and murine adipocytes and adipose tissue. Whole cell patch clamp currents were recorded during stimulation with blue light and in the presence of opsinamide (melanopsin inhibitor), U73122 (phospholipase C inhibitor), or clemizole (TRPC channel inhibitor). 3T3 L1 differentiated adipocytes were chronically exposed to blue light (4h/day for 13 consecutive days) or dark control, and assessed for changes in lipid homeostasis determined by glycerol release and Oil Red O lipid staining. Changes in adipokine secretory profiles (leptin, adiponectin) were detected using electrochemiluminescent assays.

Results: Melanopsin and TRPC1, 3, 5 variants are expressed in human and murine differentiated adipocytes. The blue light-induced current is significantly reduced in the presence of opsinamide, U73122, and clemizole (all p<0.01), indicating Gq-mediated activation of phospholipase C with subsequent activation of TRPC channels. Chronic blue light exposure causes an increase in glycerol release (day 11: p<0.01, day 14: p<0.001), and a reduction in the median lipid droplet size and total lipid droplets (both p<0.05). These changes are accompanied by significantly reduced leptin (day 11: p<0.01, day 14: p<0.001) and reduced adiponectin secretion (day 5: p<0.05, days 8, 11, 14: p<0.0001) in the blue light-exposed cells.

Conclusion: Dysfunctional adipose tissue is a hallmark of metabolic abnormalities linking obesity and diabetes. Our results suggest that regular sunlight exposure directly affects subcutaneous white adipocyte function through changes in lipid and adipokine homeostasis. These findings therefore shine light upon a novel regulatory mechanism of adipocyte biology that may in turn regulate whole body metabolism.

Keywords: adipocytes, melanopsin, light sensitivity

ADI Research Day, October 5, 2017
DIETARY INTAKE OF WOMEN IN THE HEALTHY EATING AND ACTIVE LIVING AFTER GESTATIONAL DIABETES MELLITUS TRIAL (HEALD-GDM)

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Background: Women with a history of a GDM pregnancy are at higher risk of developing Type 2 diabetes. This study aimed to describe the dietary intake, specifically the frequency of consumption and nutritional content of common foods and beverages, of women at baseline of the HEALD GDM trial.

Methods: At baseline, participants (n=42) completed demographic questionnaires and a 3-day dietary record. Participants’ intake was compared against the Daily Recommended Intake. The most commonly consumed beverages, food and composite dishes were identified. For each food and beverage, macro-nutrient (carbohydrates, protein, fat), micro-nutrient (sodium) and glycemic index and load (rating of the carbohydrate quality and quantity of foods) was described.

Results: On average, participants were 35.6 (4.2) years old and had a mean BMI of 33.1 (12.8) kg/m2. Most were Caucasian (71.4%), had a college education or higher (71.4%) and were employed full-time (50.0%). Most of the women breastfed (90.5%) and had 1 child (42.9%) or 2 children (42.9%) under the age of 8 years old. Their average daily energy intake was 2099 kcal (373). The mean daily intake of carbohydrates was 228.2g (76.4), the mean protein intake was 18.1g (4.8) and the mean fat intake was 109.6g (133.7). The average daily sodium intake was 3291.3mg (1635.4). The top 10 beverages were water, milk, coffee, tea, alcohol, soda, flavored drinks, nut milk, juice and smoothie/shake. Most beverages were low GI and GL. The top 10 foods were bread, cheese, salad, chicken, egg, sweetener, beef, cereal, potato, pasta/rice. The top 10 composite dishes were hamburgers, pizza, salad with chicken, sushi, Caesar salad, macaroni and cheese, potato salad, chicken noodle soup, chili and omelets. Most food items and composite dishes were either medium or high GI and GL.

Conclusion: Women consumed over the recommended intake of daily energy for women aged 31-50 years and the percentage of energy from fat was greater than the recommendations. The women consumed double the recommended amount of sodium. The most common foods and composite dishes were carbohydrate-based products and processed foods respectively.

Key Words: Gestational Diabetes, Diet, Intake, Glycemic Index
DIETARY INTAKE AND MICRONUTRIENT SUPPLEMENTATION IN YOUTH WITH CELIAC DISEASE (CD) WITH AND WITHOUT TYPE 1 DIABETES (T1D).

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Background: Celiac Disease (CD) occurs in 4.8% of youth with Type 1 Diabetes (T1D). Diet therapy on the Gluten-Free Diet (GFD) is necessary for CD. The GFD is characterized by a high simple sugar and limited micronutrient content, posing additional challenges with glycemic control for those with T1D. The study purpose was to describe dietary intake, and the factors influencing use of micronutrient supplements (MS) in youth with CD±T1D.

Methods: Three day food records were collected from parents of youth (3-18 years) with CD±T1D (n:14[CD]; n:10[CD+T1D]) and assessed for macro- and micro-nutrient intake, diet quality, glycemic index (GI), and glycemic load (GL) using validated methodologies. Focus group methodology was used to determine factors influencing MS use in adolescents (13-18 years) with CD±T1D, and recordings were analyzed for thematic concepts.

Results: Mean age was 11 ± 4.4(CD) and 13 ± 3.7(CD+T1D) (p:0.32). All participants had BMIs within healthy reference ranges (BMI: 17.9 ± 2.5[CD]; BMI: 19.3 ± 3.8 [CD+T1D]; p:0.61). All youth met or exceeded macronutrient requirements. Dietary intake was characterized by high GI (n:8[CD]; n:8[CD +T1D], p:0.22) and GL only in the CD group (n:12). Total sugar intake exceeded WHO recommendations in all participants (22.8±4.9%[CD]; 20.8±5.2%[CD+T1D], p:0.33). Vitamin intakes below estimated average requirements (EAR) were observed for vitamin D (n:11[CD]; n:10[CD+T1D], p:0.24), vitamin E (n:10[CD]; n:9[CD+T1D], p:0.36), folate (n:10[CD]; n:10[CD+T1D], p:1.0), calcium (n:8[CD]; n:8[CD+T1D], p:0.39), and potassium (n:13[CD]; n:10[CD+T1D], p:0.39). Multivitamins (0-500 IU of vitamin D) (n:14[CD]; n:6[CD+T1D]) and vitamin D (1000-4000 IU) (n:2[CD]; n:4 [CD +T1D]) (p:0.83) were the most popular MS taken. With MS taken into account, more youth met the EAR for vitamin D (n:9 met vs. n:5 did not [CD]; n:3 met vs. n:7 did not [CD+T1D]; p:0.21). Variables influencing MS use by adolescents included routine, health professional influence (facilitators), disease management (CD+T1D only), and lack of knowledge about the need for MS (barriers).

Conclusion: Dietary intake was characterized by excess sugar intake and low vitamin D, E, folate and calcium, which may impact micronutrient status and overall glycemic management, particularly in youth with CD + T1D. Health Professional recommendation regarding the need for MS and adolescent routine are important to ensure that adolescents with CD±T1D meet micronutrient needs.

Keywords: Celiac Disease, Type 1 Diabetes, Micronutrient Supplementation, Youth

ADI Research Day, October 5, 2017
EXPLORING THE MODULATION OF HUMAN GUT MICROBIOTA COMPOSITION AND METABOLIC FUNCTION BY ARABINOXYLAN SUPPLEMENTATION: A RANDOMIZED, PLACEBO-CONTROLLED, PARALLEL-ARM, INTERVENTIONAL STUDY

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Background: Epidemiologic and intervention studies suggest that diets low in dietary fibre (DF) are inversely associated with an increased risk of developing chronic diseases like type 2-diabetes and obesity, but intervention studies with DF are often inconsistent. The dense community of microbes that inhabit our gut has been hypothesized to contribute to the health benefits of DF and its individualized response. Microbial fermentation of DF results in the formation of short-chain fatty acids (SCFA), which are considered to have beneficial metabolic and anti-inflammatory properties, but how inter-individual variation in the compositional and functional response to specific DF-types influences the outcomes is not well understood. To address this knowledge gap, we systematically characterized the individualized gut microbial response to the DF-type arabinoxylan (AX).

Methods: Using a parallel two-arm (N=31), placebo randomized control trial; arabinoxylan or microcrystalline cellulose (non-fermentable control) was administered daily over six weeks (25g female; 35g male) in health overweight individuals without any other dietary changes. The microbial response to the DF supplementation was characterized through (I) microbiota composition analysis by 16S rRNA sequencing, and (II) the quantification of SCFA in feces and parallel in vitro fecal fermentations of the DF. Microbial diversity was calculated in QIIME and taxonomic levels were analyzed by both Ribosomal Database Project Multi-Classifier tool and UPARSE pipeline. All statistics were performed in R (3.3.2) and GraphPad Prism 6.

Results: AX reduced diversity of the fecal microbiota and induced significant shifts in the composition of specific bacterial taxa, such as a bifidogenic effect and an increase in Prevotella sp. In addition, AX administration altered the ability of the fecal microbiota to ferment this DF in vitro to SCFA; although, no significant change was observed in fecal SCFA. Both compositional shifts and SCFA response was highly individualized. Studies are underway to determine if these responses are associated with prior dietary practices and gut microbiota composition and function, and how they relate to the clinical outcomes of the study.

Conclusion: This project will provide fundamental understanding of the interactions between DF and the human microbiome, which can provide important information for the development of personalized nutritional strategies based on the characterization of the fecal microbiome.

Keywords: Dietary Fiber, Gut Microbiome, Obesity, Short-Chain Fatty Acids

ADI Research Day, October 5, 2017
COMPARTMENTALIZED REGULATION OF INSULIN SECRETION AND EXOCYTOSIS BY Kv2.1 CLUSTERS IN PANCREATIC BETA-CELLS

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Background: Exocytosis of insulin-containing granules from beta-cells is tightly regulated by ion channels, which control excitability and calcium influx. Kv2.1, which mediates the re-polarization of action potentials and interacts with Syntaxin1A, is known to target to large cell surface clusters on the soma and proximal dendrites of neurons. Previously, we have confirmed that Kv2.1 form clusters in human beta-cells, and play a role as facilitators of insulin exocytosis. It is reported that exocytosis events compartmentalized in insulinoma cells. Thus, we hypothesize that, Kv2.1 clustering may contribute to forming compartmentalized exocytosis in human beta-cells.

Methods: Patch-clamp measurement of currents and exocytosis were performed following knockdown of endogenous channels or up-regulation of recombinant channels. Live-cell total internal reflection fluorescence microscopy (TIRFM) examined Kv2.1 clusters, and their co-localization with secretory granules and granule exocytosis events in live human beta-cells, in combination with biochemical approaches to detect clustering and protein-protein interactions.

Results: Spatiotemporal detection and analysis through live-cell imaging reveals that exocytosis events in human beta-cells are clustered at hotspots. This spatial pattern, compartmentalization, is impaired in beta-cells from human donors with type 2 diabetes (T2D) with an 80% reduction of Kv2.1 mRNA and decreasing of membrane-associated Kv2.1 clusters. These impaired functions of T2D beta-cells can be at least partly rescued by up-regulating the full-length Kv2.1 which increases secretory granule recruitment, exocytosis measured by patch-clamp capacitance, insulin granule fusion events observed in live-cell TIRF, and glucose-stimulated insulin secretion. The clustering deficient mutant (Kv2.1-deltaC318), which retains electrical function and syntaxin 1A binding, is unable to rescue the insulin granule fusion deficiency in T2D beta-cells.

Conclusions: Our work identified that, Kv2.1 can directly facilitate insulin exocytosis, and that this likely depends on channel clustering. Meanwhile, exocytosis events are compartmentalized. It suggests an important micro-domain structural role for the channel at the exocytotic hotspots, which may contribute to impaired insulin secretion when Kv2.1 expression is reduced in T2D.

Key words: Exocytosis, Compartmentalization, Kv2.1, Clustering

ADI Research Day, October 5, 2017
ELEVATED IMMUNE ACTIVITY IN THE DROSOPHILA FAT BODY NEGATIVELY AFFECTS DEVELOPMENT AND METABOLISM

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Background: Immune activity and metabolic homeostasis have a tight connection. The Drosophila fat body is a multifunctional tissue and is analogous to adipose tissue and liver in vertebrates. It produces antimicrobial peptides in respond to infection via the evolutionarily conserved Immune deficiency (IMD) pathway. It also senses nutritional needs and responds through a humoral mechanism that affect organism growth, metabolism and insulin secretion. In this project, we asked how a disrupted immune signaling affects metabolism in the larva.

Method: I used our transgenic Drosophila line that has a truncated, active IMD protein (ImdCA) to induce a tissue-specific activation of IMD in the fat body. For gene expression studies, total RNA was isolated from third instar larvae and used to generate microarray probes that were hybridized to Drosophila genome 2 arrays (Affymetrix). Triglycerides and circulating trehalose from third instar larvae were also measured by calorimetric assay.

Result: To understand the effect of persistent IMD activity in the fat body, I looked at gene expression profile of larvae at third instar stage. Our KEGG pathway analysis showed that larvae with elevated IMD activity in the fat body switched from glycolysis to glycogenolysis, reduced carbohydrate metabolism, lowered insulin signaling and up-regulated apoptotic pathways. As insulin signaling regulates sugar metabolism, I looked at circulating sugar in larvae with elevated IMD activity in the fat body and found that larvae with persistent IMD activity in the fat body had a higher circulating sugar compared with controls. In addition to that, energy reservoir for triglyceride were significantly depleted in larvae with persistent IMD in the fat body. Nutritional status and development progress of the organism are correlated with each other. Therefore, I looked at development of larvae with persistent IMD in the fat body and found that they show delay in their development compared with controls. To investigate how insulin activity affects immunity, we challenged insulin mutant flies with an enteric pathogen. I found that insulin mutant flies live significantly longer in response to enteric pathogen compared with control. Interestingly, flies with an overactive insulin signaling showed a reduced lifespan in response to enteric pathogen.

Conclusion: These results outline the impact of improper immune activity on the Drosophila fat body and the consequences for development, energy storage, metabolism and insulin signaling. To advance this work, I am investigating the mechanisms involved in the effects of elevated IMD on the insulin signaling pathway in collaboration with Dr. Savraj Grewal in University of Calgary.

Key words: IMD, development, metabolism, insulin, fat body

ADI Research Day, October 5, 2017
VALIDATION OF AN INDIRECT CALORIMETRY TOOL IN ADULTS WITH CLASS II/III OBESITY

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Background: Energy needs are determined by total energy expenditure (TEE), or the number of kilocalories (kcal) used each day. As measurement of total energy expenditure is costly and difficult, energy recommendations are often estimated by calculating resting energy expenditure (REE), the largest component of TEE. However, predictive equations to estimate REE are often inaccurate for individuals with obesity, a population with high rates of comorbidities (such as diabetes), which would benefit from accurate energy prescription. Measuring REE in clinical practice is not always realistic due to space limitations and equipment cost. The objective of the current analysis was to assess the accuracy and reliability of a portable indirect calorimeter, the Fitmate GS (with ventilated hood), against the state-of-the-art whole-body calorimetry unit (WBCU) in individuals with class II/III obesity (body mass index, BMI ≥ 35 kg/m²).

Methods: Adults with class II/III obesity and aged 18-55 years were recruited for the study. REE values were obtained from WBCU and compared with Fitmate GS measurements performed on the same day. Fitmate GS measurements were completed twice for each participant. A brief medical history (medical conditions, current medications and activity level), anthropometrics (height, weight, waist and hip circumference) as well as basic demographic data (age, sex and ethnicity) were collected for each individual. Group-level agreement between the Fitmate GS and WBCU measurements were assessed via dependent samples t-test. Bland-Altman analysis was used to assess both group-level (bias, average difference) and individual-level agreement (limits of agreement, bias ± two standard deviations). The minimum and maximum differences were also reported to contextualize the results to clinical practice. Test-retest reliability was assessed using intraclass correlation coefficient with two-way random effects.

Results: Preliminary data for 15 participants (BMI = 41.4 ± 7.8 kg/m²; age = 36 ± 10 years) was collected (for a total of 35 needed for study completion). On average, REE measurements from the Fitmate GS were lower than the WBCU (1718 ± 358 versus 2009 ± 381 kcal/day, p = 0.003) and individual values differed from – 10 to – 680 kcal/day. Bland-Altman analysis showed an overall underestimation of REE (bias: -291 kcal/day) and wide limits of agreement (-609 to +28 kcal/day). Comparison of two separate Fitmate GS measurements from the same subject showed a difference up to -770 kcal. The intraclass correlation coefficient was 0.769 (“moderate” agreement according to the literature) with 95% confidence interval from 0.454 to 0.915.

Conclusion: Our preliminary finding showed the Fitmate GS was not an accurate or reliable tool for measuring REE on a group and individual level in a sample of adults with class II/III obesity. While our increasing sample size may reveal better performance on a group level, results from such machines should be interpreted with caution at this time.

Key words: Resting energy expenditure, obesity, indirect calorimetry, nutrition assessment
EXPLORING γδ T CELL POPULATIONS IN HEALTHY CHILDREN: WHAT IS NORMAL?

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BACKGROUND: There is mounting evidence in mouse models that γδ T cells are involved in immune responses in Type 1 diabetes (T1D). However, studying this rare population in blood samples in small pediatric samples is challenging, as is accessing controls. Adult control data have been established using standardized flow cytometry phenotyping in the European OneStudy, but comparable pediatric reference ranges do not exist. Our group had the opportunity to collaborate with the clinical hematology laboratory to obtain normal pediatric samples. Our objective is to establish a reference dataset to be available for pediatric studies using comprehensive flow cytometry panels with fresh whole blood. This study is also a useful trial of this methodology for potential implementation in the clinical laboratory. Beckman Coulter provides extensive standardized panels to explore T and B cell markers. One such group of markers are those for γδ T cells and their subsets Vd1 and Vd2.

METHODS: Using 700uL of blood, DuraClone IM flow cytometry phenotyping was performed to garner a comprehensive immune phenotype of pediatric patients ranging from 66 days to 16 years of age (n=10).

RESULTS: Samples were tested in five 10-colour immunophenotyping panels. The overall number of CD3+ T cells, including γδ T cells, decreases over the pediatric age spectrum, while the % of each population of cells remains constant. There is a trend indicating a decreasing ratio of Vd1 to Vd2 γδ T cells with increasing age of the pediatric controls.

CONCLUSION: The decreasing number of γδ T cells with age is expected as lymphocyte counts decrease with age. While the sample size is limited and this cell population is known to fluctuate, there does appear to be a relationship between aging and the ratio of the Vd1 to Vd2 γδ T cell subsets. This may be an important consideration in the investigation of the role of γδ T cells in T1D, as much of the research to date has been in mouse models and it is known that these populations are not represented in the same manner in humans. This standardized TCR flow panel may be a useful tool for gaining more insight into the subsets of γδ T cells at the onset of T1D or after islet cell transplantation. This unique partnership between the research and clinical labs provides a valuable opportunity to define pediatric patients' immune phenotype and clinical applications of this methodology. We will continue to test additional samples and investigate this and other trends across the age spectrum.

KEYWORDS: Flow cytometry phenotyping, γδ T cells, Type 1 diabetes, islet transplantation

ADI Research Day, October 5, 2017
THE TYROSINE PROTEIN KINASE LYN IS ESSENTIAL FOR MAINTAINING BETA-CELL PROLIFERATION, SURVIVAL AND ISLET STRUCTURE

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Background: Diabetes manifests after a reduction in beta-cell mass. It is therefore important to identify the molecular mechanisms governing beta-cell life and death. Our previous study, investigating GLP-1 signaling in beta-cells, revealed a key role for a Src member in the regulation of beta-cell mass. However, the identity of this Src family member remained elusive. We herein sought to precisely identify the Src family member that mediates GLP-1 action, and examine its role in the regulation of beta-cell mass and function.

Methods: We measured the expression and activity of Src family members in INS cells and human islets. We also performed gain- and loss-of-function experiments for each Src member, using virus-mediated overexpression and siRNA-mediated knockdown respectively. We further explored the role of Lyn in vivo using beta-cell specific Lyn knockout mice (bLynKO). We thus investigated the consequences of Lyn deletion on glucose homeostasis and islet morphology.

Result: Our results show that pancreatic beta-cells express three Src family members: c-Src, Lyn and Fyn. Of those, only c-Src and Lyn were activated by the beta-cell growth factor GLP-1. Overexpression and down-regulation of c-Src, Lyn and Fyn in INS cells unraveled a unique role for Lyn in beta-cell proliferation and survival. Indeed, knockdown of Lyn provoked beta-cell death, whereas Lyn overexpression prevented apoptosis in both INS cells and human islets. Similarly, knockdown of Lyn blunted INS cell proliferation, whereas Lyn overexpression resulted in increased proliferation. Pharmacological activation of Lyn using MLR1023 reiterated the effects of Lyn gain-of-function, in addition to increasing insulin release. bLynKO mice displayed altered islet architecture and reduced in islet mass. Although profound, these changes did not translate into impaired glucose tolerance, suggesting that loss of Lyn is not sufficient to curtail beta-cell function.

Conclusion: Our study identifies and characterizes Lyn as a novel regulator of beta-cell mass. As such, Lyn could represent a promising molecular target for diabetes treatment.

Keywords: Lyn, c-Src, tyrosine protein kinases, beta-cells, proliferation, apoptosis.
Vitamin D directly inhibits TRPV1 channels and reduces the activation of naïve T-cells.

Recent evidence suggests that Vitamin D plays an important role in regulating immune T-cell activity and may be involved in reducing the risk of Type 1 Diabetes (T1D) by dampening naïve T-cell activation and/or the inflammatory response. However, the exact mechanism of how Vitamin D modulates the activation of naïve T-cells is still unknown. Traditional pharmacology suggested that Vitamin D acts almost exclusively on the Vitamin D receptor (VDR). However, the very low or absent VDR expression levels in naïve T-cells suggest that any effects of Vitamin D on naïve T-cell activation may be VDR-independent. In this regard, it has been shown that TRPV1 channels activation is necessary for naïve CD4+ T-cell activation. Interestingly, our electrophysiological data demonstrate that both the inactive circulating 25OHD and the active 1,25OHD are inhibitors of TRPV1 channels at physiologically relevant concentrations (100 nM). Therefore, we hypothesized that 25OHD and 1,25OHD could modulate naïve T-cell activation through direct inhibition of TRPV1 channels. In this study, we characterized the effects of 25OHD and 1,25OHD on 1) TRPV1 channels and 2) the activation and cytokine production of naïve mouse T-cell through flow cytometry analysis. Our data illustrate that 25OHD and 1,25OHD are effective inhibitors of TRPV1 channels in the 50-200 nM physiological range, and this inhibition effect depends on intracellular calcium levels. Our results also show TRPV1 channels are important in naïve T-cell activation, and that both 200 nM 25OHD and 200 nM 1,25OHD significantly reduce TNF alpha/INF gamma and IL2/IL4 production after 24 hours activation by anti CD3/CD28 on enriched mouse CD4+ T-cells. These results support the concept that vitamin D could directly inhibit TRPV1 channels in naïve T-cells, reducing their activation in a VDR-independent manner. Our findings further advance knowledge on the underlying cellular mechanism by which vitamin D may beneficially dampen naïve T-cell activation in autoimmune diseases such as T1D.
GLUCOSE RESPONSES TO ACUTE EXERCISE IN PREGNANCY: A SYSTEMATIC REVIEW AND META-ANALYSIS

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BACKGROUND: The objectives of the systematic review and meta-analysis were 1) to assess the glycemic responses to acute prenatal exercise in women with-and-without diabetes in pregnancy (gestational diabetes mellitus [GDM], Type 2 diabetes [T2D]), and 2) to assess the proportion of hypoglycemia in response to prenatal exercise.

METHODS: Online databases via Ovid and EBSCO platforms were used to perform a structured search up to January 5, 2017 for publications reporting acute prenatal exercise and glucose responses in women without contraindication to exercise. Pre vs. during/post-exercise mean differences (MD) were pooled using a random effects model, and subsequent meta-regression analyses were performed to compare the outcome variable to volume of exercise (MET-minutes per session). Hypoglycemia incidence (author defined) was used to estimate the proportion of hypoglycemic events in response to exercise. Grades of Recommendation, Assessment, Development and Evaluation (GRADE) methodology was used to assess the quality of evidence.

RESULTS: 22 studies were eligible for inclusion in the current meta-analysis. Despite “very low” quality evidence that an acute bout of prenatal exercise was associated with a 0.94mmol/L decrease in blood glucose (BG) values during exercise (95% [CI] -1.18, -0.70), and 0.80mmol/L post-exercise (95% [CI] -0.97, -0.56), the proportion of hypoglycemia in response to acute prenatal exercise was low (mean: 0.00, 95% [CI] 0.00, 0.04). After stratifying studies comparing women with-and-without diabetes, we observed larger decreases in BG values post-exercise in women with diabetes (MD: -1.42, 95% [CI] -1.69, -0.56) compared to women without diabetes (MD: -0.61, 95% [CI] -0.81, -0.41). Finally, meta-regression analyses demonstrated a dose-response relationship between volume of prenatal exercise and glycemic responses during exercise ($p=0.007$), but not post exercise ($p=0.276$).

CONCLUSION: Relatively low proportion of hypoglycemia in response to prenatal exercise in women with-and without diabetes suggests that maternal decreases in circulating BG values are within euglycemic ranges following an acute bout of exercise.

KEY WORDS: Pregnancy, Exercise, Hypoglycemia, Glucose, Diabetes
MOUSE ISLETS CO-CULTURED WITH ADIPOSE MESENCHYMAL STROMAL CELLS IMPROVES ISLET FUNCTION

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Background: Islet transplantation (IT) is a current clinical treatment for select patients with type 1 diabetes, however, it may not be a permanent solution to correct hyperglycemia due to the progressive loss of \( \beta \)-cell mass. A potential strategy to prevent \( \beta \)-cell loss and improve engraftment is through the co-transplantation of islets with multipotent mesenchymal stromal cells (MSCs). As self-renewing stem cells, MSCs exhibit immunomodulatory and regenerative properties. Previous studies evaluating the use of bone marrow-derived MSCs (BM-MSCs) have reported improved islet engraftment. An alternative source of MSCs are derived from adipose tissue (adipose-derived, or AD-MSCs), which are more easily accessible than BM-MSCs. To date, limited research has evaluated the utility of AD-MSCs and their potential to augment engraftment in islet transplantation. The objectives of the current study are to evaluate if: (i) co-culture of human AD-MSCs with murine islets will enhance in vitro islet function; and (ii) co-transplantation of AD-MSCs and murine islets will improve islet engraftment in an immunocompromised murine islet transplantation model.

Methods: Mouse islets were isolated from BALB/c donors and cultured for 48 hours either by themselves or in a co-culture with AD-MSCs using an islet to AD-MSCs ratio of 1:300 or 1:2000. In vitro islet viability and function, apoptosis, and insulin secretion were assessed through syto green/ethidium bromide membrane integrity staining, TUNEL immunohistochemistry, and static glucose-stimulated insulin secretion assay (sGSIS), respectively. To evaluate in vivo islet engraftment, a marginal dose of 150 BALB/c islets was transplanted immediately post-isolation under the renal capsule of diabetic, immunocompromised Rag\(^{-/-}\) recipients, either alone or co-transplanted with AD-MSCs (1:2000 islet:AD-MSCs). Non-fasting blood glucose was monitored three times a week, and at 60 days post-transplant, in vivo graft function was assessed by an intraperitoneal glucose tolerance test (IPGTT). To determine graft-dependent euglycemia, a recovery nephrectomy was performed. Islet-bearing grafts were analyzed for insulin content and cyto-architecture by histological assessment.

Results: Post-culture in vitro analysis revealed that islets co-cultured with both AD-MSCs ratios exhibited a significant increase in both sGSIS response (p<0.05 and p<0.05; One-way ANOVA) and membrane integrity (p<0.05 and p<0.05; One-way ANOVA) compared to control islets cultured alone. Immunohistochemistry TUNEL staining revealed that control islets exhibited a significant increase in apoptosis when compared to islets cultured with both ratios of AD-MSCs (p<0.05 and p<0.05; One-way ANOVA). When transplanted immediately post-isolation, control islets' percent euglycemia (100%: 4 of 4) was significantly higher than islets co-transplanted with AD-MSCs (1:2000) (50%: 7 of 13).

Conclusion: In vitro analysis revealed improved islet function for islets cultured for 48 hours with AD-MSCs compared to islets alone. Islets co-transplanted with AD-MSCs immediately post-isolation did not confer significant improvements in engraftment outcomes. Future work will assess whether engraftment efficacy is improved when islets are co-cultured for 48 hours with AD-MSCs. Overall, the co-culture of islets with AD-MSCs may be a promising approach for improving islet function and subsequent engraftment outcomes.

Key words: Islet transplantation, Mesenchymal stem cells, Co-culture

ADI Research Day, October 5, 2017
SENPI IN COMPENSATION AND FAILURE OF INSULIN SECRETION WITH HIGH-FAT-DIET

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Background & Aim: Pancreatic β-cells adjust their ability to secrete insulin according to the body's needs. While glucose-induced membrane depolarization is required for the initiation of secretion, the generation of several coupling factors regulates the amplitude of insulin release. Our recent studies identified the deSUMOylating enzyme SENP1 as a key factor required downstream of metabolic coupling factors to amplify insulin secretion, while others have suggested that SUMOylation controls the activity of the G-protein coupled glucagon-like peptide-1 (GLP-1) receptor. The deletion of SENP1 reduced glucose-induced-insulin secretion, and causes glucose intolerance in mice. Interestingly, increasing SENP1 rescues insulin exocytosis in human β-cells from donors with type 2 diabetes (T2D). However, the involvement of SENP1 in the regulation of β-cell function in the progression and establishment of T2D remains unclear.

Methods: WT mice were put on chow diet (CD) and high fat diet (HFD) for 2-days, 7-days, 4-weeks, or 8-weeks. Islet-specific SENP1 KO mice (SENP1-iKO) mice, generated by crossing floxed-SENP1 mice with the Pdx-Cre line, were fed with HFD for 8 weeks.

Results: The exocytotic response of isolated β cells from WT mice was increased after 2-day, 7-day, and 4-week HFD compared to β cells from mice on CD. This is consistent with an acute compensatory response of the WT mice to HFD. The body weight of SENP1-iKO mice was similar to WT control littermates during 8 weeks of HFD, however the SENP1-iKO mice have elevated fasting blood glucose at 8 weeks. Insulin tolerance was unaltered, however the fasting plasma insulin was low in SENP1-iKO mice. Although glucose-stimulated insulin secretion from SENP1-iKO islets was similar to WT controls, preliminary immunohistochemistry shows that deletion of SENP1 results in reduced islet size after a HFD. In addition, β-cells from SENP1-iKO mice showed loss of Exendin-4 potentiated exocytosis compared to control littermates, consistent with their impaired oral (but not intraperitoneal) glucose tolerance at 8 weeks HFD.

Conclusion: Single β-cells respond to a HFD by acutely up-regulating their secretory function, but then ultimately decompensating to a state of impaired exocytotic capacity in the longer-term. While further work will be required to determine whether the SENP1 is required for acute compensation, loss of this SUMO protease leads to a worsening of glucose tolerance over time. This might be due to impaired insulin secretion and islet mass adaptation caused by impaired GLP-1 receptor signaling.

Key words: SENP1, compensation, HFD

ADI Research Day, October 5, 2017
CAN NEWBORN PIG ISLETS SURVIVE IN CELLULOSE NANOFIBROUS MEMBRANES?

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Background: Islet transplantation is being considered as an alternative treatment for Type 1 Diabetes Mellitus (T1DM). Human donor shortage limits this method; therefore, our group is studying neonatal porcine islets (NPI) as an alternative source. A major problem documented with islet transplantation is the loss of extracellular membrane (ECM) during isolation and the post-operative immune response against the transplant. Cellulose nanofibrous membranes have the potential to increase the survival of islets and enhance their function post transplant. In this study, we tested this hypothesis by placing NPI inside the membrane and evaluating function after exposure to cytokines in vitro.

Methods: NPI were isolated from 3-day-old pigs (n=7) and cultured at physiological conditions for 7 days in Ham’s F10 Nutrient Mix medium. The islets were collected and 2000 Islet Equivalents (IEQ) were placed in culture or membrane bags made of cellulose with and without collagen. The membrane bags were sutured to close and incubated in Ham’s F10 medium for 24 hours. A glucose-stimulated insulin secretion assay (GSIS) was then conducted on the islets in order to evaluate the function. In addition, samples of islets were collected to determine the DNA content, cell viability using TUNEL assay, and presence of β and α cells using immunostaining. Further, islets were also exposed to human IL-1β, IFN-γ, and TNF-α cytokines separately and together, at the concentrations of 25 ng/µL, 250 ng/µL, 250 ng/µL respectively. After culture for 24 hours, islets were collected, and assessed for their function, DNA content, viability, and cell composition.

Results: Preliminary tests with membranes with and without collagen found that there was no significant difference (p>0.05) between the cellular insulin produced through islets housed in the collagen bag versus the free islets. However, when tested with the glucose tolerance test, the islets in the collagen bag secreted insulin in a more similar manner to the free islets than the islets in the non-collagen bag. We then continued experimentation with the cellulose plus collagen bag, and found comparable viability of bagged to free islets (>95%), and comparable insulin/glucagon positive immunostaining. In the presence of cytokines, gross morphology through Dithizone dye revealed the bags show a trend of yielding more intact islets after culture. Results for GSIS assay pending.

Conclusion: The nanofibrous membrane provided a scaffold that encompassed the islets, offering a type of membrane to replace the ECM lost during isolation. The similarity in function and viability between the free islets and islets in the bag, gives potential for islet transplant while contained in a nanofibrous membrane, without impact to function or viability. The trend of bags yielding more intact islets after cytokine exposure provides an interesting framework for protection from immune response, including the attachment of specific antibodies to the membrane.

Keywords: Nanofibrous Membrane, Scaffold, Cytokines, Islets, Xenotransplantation

ADI Research Day, October 5, 2017
THE EFFECTS OF HYPOXIA ON NEONATAL PORCINE ISLETS

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Background: Islet transplantation is being considered as an alternative treatment for type 1 diabetes mellitus. However, islet viability is greatly decreased during the transplantation process due to, among other factors, hypoxic injury leading to islet cell death. It has been shown that neonatal porcine islets (NPI) have natural resistance to hypoxic injury compared to adult porcine islets (API). It is hypothesized that islet precursor cells (immature islet cells) within the NPI are responsible for providing this protection, as they do not undergo apoptosis when stressed by hypoxia. This study aims to further evaluate the effects of hypoxia on neonatal porcine islet cells, as well as to determine whether or not cyanidin-3-O-glucoside (C3G) a naturally derived antioxidant, has any effect on the islets.

Methods: Neonatal porcine islets (n=4) were isolated and cultured at 37°C, 95% air, 5% CO2 for seven to eight days in Ham’s F10 nutrient medium. The islets were then transferred into 6-well plates with each well containing one thousand islet equivalent (IEQ) in Ham’s F10 nutrient medium. The islets were either left untreated or treated with 1μM C3G. After 24h of culture in physiological condition with or without C3G, the islets were moved to incubators containing 1% oxygen, 3% oxygen, and 20% oxygen - the latter being normal conditions. As controls, one thousand IEQ were treated with Rapamycin, an apoptosis-inducing drug for 24h, and one thousand IEQ were treated with H2O2, a reactive oxygen species known to induce necrosis in islets, two hours before collection. After 24h the cells were collected and their viability and morphology were assessed using Annexin Cy3 Apoptosis Detection Kit (TUNEL assay) and Dithizone staining, respectively. Immunohistochemical staining of CK7 was also performed on the islets to show the presence of ductal, or precursor islet cells. The same experiments conducted on API.

Results: NPI from all hypoxic conditions expressed 90% to 94% live cells, 4% to 6% necrotic cells, and 2% to 4% apoptotic cells. No significant differences were observed between untreated and C3G-treated islets within and between all hypoxic conditions compared using two-way analysis of variance. All NPI exposed to hypoxia, Rapamycin and H2O2 were positive for CK7. No statistically significant difference found in regards to CK7 expression on NPI between any conditions. NPI exposed to H2O2 + C3G showed significant rise in the number of live cells and significant decrease in the number of necrotic cells when compared to NPI exposed only to H2O2. Dithizone staining showed no significant differences between untreated and C3G-treated NPI in all conditions. Statistical analysis and immunohistochemical staining of API are still pending.

Conclusion: Islets exposed to hypoxic conditions are not negatively affected by C3G. Moreover, C3G seems to offer protection to NPI exposed to reactive oxygen species, such as H2O2. Therefore, we can conclude that NPI treated with C3G are not negatively affected when exposed to hypoxia and that their natural resistance to hypoxic injury remains present.

Key Words: Hypoxia, Islet Transplantation, Apoptosis, Necrosis, Precursor Cells

ADI Research Day, October 5, 2017
INVESTIGATION OF ABO TOLERANCE IN A MOUSE MODEL FOLLOWING NEONATAL TREATMENT WITH A NOVEL A-ANTIGEN GLYCOCONJUGATE

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Background: ABO-incompatible heart transplantation (ABOi HTx) is safe during infancy and allows increased donor access. Post-ABOi HTx, B cell tolerance develops to donor blood group antigen(s) by mechanisms not fully defined. We developed A-transgenic mice (A-Tg, both C57BL/6 (B6) and BALB/c (BALB) backgrounds) that express A-antigen on vascular endothelium and erythrocytes (RBCs) and demonstrated A-antigen specific tolerance following HTx into young (4 wk) wild-type (WT) B6 mice. Intentional induction of tolerance to A/B-antigen(s) in infancy may allow later ABOi HTx. Here, we explored intentional tolerance induction using a novel bifunctional glycoconjugate (GC) displaying AG10, a small molecule that binds transthyretin and increases the half-life of small molecules in serum, and human A subtype II antigen (A(II)-AG10).

Methods: Neonatal (<24 hours after birth) WT BALB mice were intravenously injected with 100 µg A (II)-AG10 GC (synthesized and characterized in-house; n=7) or left untreated (n=7). At 5 weeks of age, intraperitoneal injections (100 µL) of human A-RBC membranes (20% vol/vol) were administered weekly (5x) in an attempt to elicit anti-A antibody. Serum anti-A antibodies were assessed by hemagglutination and ABH microarray (ABH subtype I-VI) assays.

Results: A-sensitization resulted in high-levels of IgM and IgG antibody specific to A(II) with no significant difference between A(II)-AG10 GC treated or untreated groups (IgM, p=0.944; IgG, p=0.528). Following A-sensitization, compared with the untreated group, A(II)-AG10 GC treatment resulted in similar levels of antibodies to A-subtypes I-VI (IgM, p=0.185; IgG, p=0.185); however, the treatment group displayed overall greater IgM antibody production against all ABH antigen subtypes (p<0.05).

Conclusion: Neonatal treatment with A(II)-AG10 GC in this model did not result in tolerance to A (II)-antigen. Ongoing studies are assessing tolerance using A-GC containing CD22L, as CD22-CD22L interactions have been shown to be important in B cell tolerance induction. In addition to A-GC trafficking studies, specific parameters of our protocol, such as amount, route, and timing of treatment injections, are also being explored.

Keywords: B cell tolerance, glycoconjugate, transplantation, ABO blood groups

ADI Research Day, October 5, 2017
DEVELOPMENT OF A RAPID ASSAY TO ASSESS POTENCY OF THERAPEUTIC REGULATORY T CELLS (TREGS)

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Background: Regulatory T cells (Tregs) have been proposed as a therapy to prevent and/or treat transplant rejection, graft-vs-host disease and autoimmune disease due to their immunosuppressive ability. Our lab has shown that abundant, highly suppressive Tregs can be isolated and expanded from discarded human thymus, routinely removed during pediatric cardiac surgery. Current suppression assays to assess the potency of expanded Tregs is based on suppression of T cell proliferation over four days, a timeframe that limits clinical use. We sought to establish a one-day suppression assay involving the suppression of T cell cytokine production by expanded Tregs. We hypothesize that re-stimulation of activated T cells will cause rapid cytokine production within a few hours which can be tested as a substrate for suppression by the addition of expanded Tregs.

Methods: For this pilot study, peripheral blood mononuclear cells were isolated from blood of healthy volunteers (n=4). T cells were isolated by magnetic bead separation, stimulated using anti-CD3/CD28 beads (ratio 10 cells:1 bead), and cultured for 7 days. Supernatant was obtained daily and a cytokine assay (MSD Multispot Assay) was performed. In addition, T cells were stimulated with anti-CD3/CD28 beads for two days. On day 2, cells were collected and washed. One group of stimulated T cells was re-stimulated and the other was not re-stimulated. Supernatant was taken at 2, 4, and 6 hr timepoints and assessed by cytokine assay.

Results: Cytokine concentrations peaked at day 3 and 6 for IFNγ (range: 1567-2488 pg/mL), and day 2 for IL-10 (7.8-14 pg/mL), IL-2 (259-353 pg/mL) and TNFα (78-100 pg/mL). Since the highest production of most cytokines occurred on day 2, we performed re-stimulation on this day. After re-stimulation of the previously stimulated T cells, cytokine production began as soon as 2hr after re-stimulation with a steady increase in cytokine production from 2 hr to 6 hr. The re-stimulated T cells secreted higher levels of cytokines than the non-re-stimulated T cells at each timepoint.

Conclusion: Re-stimulation of activated T cells resulted in rapid production of cytokines on the scale of hours indicating that cytokine analysis of re-stimulated T cells may be exploited for the development of a one-day suppression assay. In future experiments, re-stimulated T cells will be cultured with or without expanded Tregs to assess suppression of cytokine secretion. A reproducible rapid suppression assay would be a powerful tool to check the potency of therapeutic Tregs for clinical use.

Keywords: Cell therapy, Immunology, Transplantation, Autoimmunity, Regulatory T cell

ADI Research Day, October 5, 2017
DIETARY ASSESSMENT OF WOMEN WITH POLYCYSTIC OVARIAN SYNDROME

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Background: Polycystic Ovarian Syndrome (PCOS) is an endocrine-metabolic disease that affects up to 10% of Canadian women and includes symptoms of infertility, acyclicity and hyperandrogenism. Women with PCOS have a high incidence of the metabolic syndrome (MetS) and are at increased risk of Type 2 Diabetes and Cardiovascular Disease (CVD). The etiology of PCOS is linked to underlying genetic factors and diet-lifestyle associated weight gain and obesity. The MetS, in particular a high body mass index (BMI >30 kg/m2) has been shown to exacerbate hyperandrogenemia, infertility, insulin resistance, dyslipidemia and mental health in women with PCOS. Dietary intake and lifestyle contribute to weight gain and obesity in PCOS, however there this is limited data available on the dietary intake of women with PCOS in Alberta and Canada. The aim of this pilot study was to assess the dietary intake of high-risk obese women with PCOS recruited from Edmonton, Alberta and to compare their dietary intake with Health Canada's Food Guide recommendations.

Methods: Participants were women aged 18-30 yrs diagnosed with PCOS and were recruited from the wider Edmonton area, Alberta, and Division Endocrinology, U of A hospital, as part of a clinical trial study, n=19 (HC6-24-C191998). Inclusion criteria consisted of PCOS diagnosis using NIH-AEPCOS criteria, BMI >25 kg/m2, elevated fasting plasma triglycerides (>150mg/dL), impaired insulin sensitivity (glucose 100-125 mg/dL) and/or diagnosed with T2D (glucose >126 mg/dL). Exclusion criteria included pregnancy, lactating, use of medications that impact lipid metabolism and exclusion of other endocrine disorders. A 3-day dietary record was used and reviewed with the study participant by a registered dietitian. Dietary data was analysed using Food Processor (v11.0.124.) and compared to Health Canada's Food Guide and recommendations for women aged 18-30 yrs with low active physical activity and BMI 18.5-24.9 kg m2, including average macronutrient distribution range (AMDR) for macronutrients, total kcal, fibre, sugar and fruit -vegetable intake.

Results: The PCOS participants met the AMDR for the dietary macronutrients: protein (10-35%), carbohydrates (20-35%) and fats (45-65%), and had similar intake compared to recommendations for this population. More than 57% and 52% of participants exceeded the recommendations for dietary intake of total kcal (range 1251 - 3471 vs 1900-2100 kcal/d) and total sugar (range 16 to 230 vs 100g/d). Recommendations for daily total fibre intake and servings of fruit and vegetables were not met by >68% (range 10 - 49g/d) and >57% (range 0 -13 servings/d) of participants, respectively.

Conclusion: These preliminary findings in Albertan women with PCOS show dietary AMDR recommendations were met, however more than 50% of participants exceeded dietary total kcal, fat and sugar intake and did not meet fibre and fruit-vegetable dietary intake recommendations. Future analyses of dietary intake will include micronutrients, healthy eating index, and data will be used to develop specific dietary interventions and strategies to target dietary intake and body weight management in Albertan overweight-obese women with PCOS.

Key words: Polycystic ovarian syndrome, obesity, metabolic syndrome, diet intake and analysis

ADI Research Day, October 5, 2017
Background: Polycystic Ovary Syndrome (PCOS) is an endocrine-metabolic disease that affects up to 18% of women of reproductive age and is diagnosed by the presence of acyclicity, hyperandrogenism and/or cystic ovaries. PCOS is highly associated with obesity, insulin resistance and dyslipidemia and increases the risk of early development of Type 2 Diabetes and Cardiovascular Disease (CVD). Atherogenic dyslipidemia occurs in >70% of women with PCOS and includes high fasting and non-fasting plasma TG and ApoB-cholesterol remnants. Diet and lifestyle is the first-line intervention and metformin, which is commonly prescribed for impaired glucose sensitivity, have been shown to not reduce blood lipids in women with PCOS. Furthermore, treatments for dyslipidemia are limited due to safety and efficacy in young women of reproductive age with PCOS. Dietary supplementation with fish oil (rich in EPA and DHA) has been used in obesity, MetS and Type 2 diabetes to reduce fasting and non-fasting TG, but the effectiveness in conditions of PCOS and hyperandrogenism have not been elucidated. The aim of this study was to determine the effect of dietary fish oil supplementation compared to metformin and fish oil combination treatment on fasting and non-fasting plasma lipids and apoB-remnant lipoprotein metabolism in obese young women with PCOS.

Methods: Participants were women aged 18-30 yrs diagnosed with PCOS and recruited from Edmonton area, Alberta, and Division Endocrinology, U of A hospital, as part of a randomized parallel study design with intervention arms of 12 wk duration: 1) dietary supplementation with fish oil (containing 2400mg EPA+ 1200mg DHA/d), 2) fish oil + metformin (1500mg/d) (HC6-24-C191998). Inclusion criteria consisted of PCOS diagnosis using NIH criteria, BMI >25 kg/m2, elevated fasting plasma triglycerides (>150mg/dL), impaired insulin sensitivity (glucose 100-125 mg/dL) and/or diagnosed with T2D (glucose >126 mg/dL). Exclusion criteria included pregnancy, lactating, use of medications that impact lipid metabolism and exclusion of other endocrine disorders. Fasting and non-fasting plasma lipids (TG and CHOL) and apoB-cholesterol remnants (apoB48) following a high-fat meal challenge were measured by calorimetric and SDS-PAGE ELISA methods, and area under the curve (AUC and incremental, iAUC) analyses were performed (Prism 5.0).

Results: Our pilot data shows fish oil and metformin (n=5) treatment compared to fish oil alone (n=5) may reduce to a great extent fasting plasma TG (147.1±19.1 vs 205.3±30.9 mg/dL) and apoB48 (8.4 ±1.2 vs 5.3±0.24 ug/ml). Fish oil and metformin and fish oil alone appear to similarly reduce non-fasting total AUC for plasma TG (approx.-30%, 1794±390 baseline vs 1548±479 post-intervention for fo+met) and B48 (approx. -15%, 88.9±5.2 baseline vs 57.48±1.9 post-intervention for fo+met) and similar results were observed for iAUC TG and iAUC B48. No effect of treatments on fasting or non-fasting plasma total cholesterol was observed.

Conclusion: These preliminary analyses demonstrate the potential effectiveness of fish oil and the combination of fish oil and metformin to reduce hypertriglyceridemia and apoB-remnant lipoproteinemia in obese young women with PCOS.

Keywords: Polycystic ovary syndrome, atherogenic dyslipidemia, triglycerides, apoB-remnants

ADI Research Day, October 5, 2017
SYMPATHETIC AND CARDIOVASCULAR REGULATION FOLLOWING GLUCOSE INGESTION

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Background: Acute increases in blood glucose are associated with heightened sympathetic nerve activity (SNA) in humans. Animal studies have implicated a role for the peripheral chemoreceptors in this response, but this has not been examined in humans.

Methods: Heart rate (HR, ECG), cardiac output (CO, Model Flow), mean arterial pressure (MAP, photoplethysmography), and total peripheral resistance (TPR; MAP/CO) were collected in 11 participants (8 female); SNA was recorded in a subset of 5 participants (4 female). Following baseline (0 min), participants ingested 75g of glucose followed by repeated measurements at 20 min, 40 min, and 60 min. At each time-point, 100% oxygen was delivered (4 min) to deactivate the peripheral chemoreceptors.

Results: Blood glucose levels increased from baseline (5.46±0.72mmol/L) to 12.40±1.25mmol/L at 60 min post ingestion. There was a positive correlation between blood glucose levels and burst frequency (r²=0.494; p=0.027). Total SNA (normalized burst amplitude x burst frequency) was significantly increased from baseline (783±340AU) at 20, 40, and 60 min following glucose (1270±374 AU, 1307±632 AU, and 1534±902 AU, respectively; p<0.05). Oxygen attenuated the total SNA increases at 20 and 60 min (-224±81 AU and -245±101 AU, respectively; p<0.05). HR was increased (p<0.01) at 40 and 60 min following glucose (62.66±6.25 bpm to 70.12±7.27 bpm and 71.55±8.16 bpm, respectively) as was CO (5.84±1.02 L/min to 7.06±1.40 L/min and 7.17±1.38 L/min at 40 and 60 min, respectively; p<0.05). Both of these responses were blunted during hyperoxia at 60 min (p<0.05). In contrast, TPR was reduced from baseline at 40 and 60 min (16.28±2.89AU to 13.46±2.72 AU and 12.76±1.80 AU; p<0.05).

Conclusion: Our results suggest that sympathetic activity significantly increases following glucose ingestion due in part to peripheral chemoreceptor activation. Changes in SNA appear to be dissociated from concurrent changes in TPR suggesting blunted neurovascular transduction following acute glucose ingestion.

Key words: sympathetic regulation, peripheral chemoreceptors, blood glucose

ADI Research Day, October 5, 2017
FRAILTY INFLUENCES RISK FOR DEPRESSION, REDUCED QUALITY OF LIFE (QOL) AND RISK OF HOSPITALIZATION IN AN AMBULATORY POPULATION WITH DIABETES MELLITUS (DM) AND CHRONIC KIDNEY DISEASE (CKD)

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Background. Frailty is a syndrome characterized by a decline in physiological reserves and functions that increases vulnerability to adverse health outcomes and is highly prevalent in elderly clinical populations. Frailty, low vitamin D status and low lean mass have been associated with increased risk for morbidity and mortality and reduced quality of life (QoL) in the elderly. We hypothesized that suboptimal vitamin D status combined with reduced lean body mass would contribute to depression, frailty and increased hospital utilization in adults with DM and CKD.

Methods. We prospectively studied body composition (Dual X-ray Absorptiometry), vitamin D status (serum 25(OH)D3), frailty (Edmonton Frail Scale), depression (Major Depression Inventory: MDI) and QoL (SF-36) in adults with DM and CKD (69.5 ± 8.3 years) over 3-5 years using validated methodologies. Hospitalization (total, type) was reviewed in medical records.

Results. Out of 42 patients with CKD and DM, a total of 7 (16.6%) were defined as frail. A lower Appendicular Skeletal Muscle Index (ASMI) (p=<.05), Glomerular Filtration Rates (GFR) under 60 ml/min/1.73m2 (<.05) and depression (p=<.0001) were associated with frailty. Frailty was also associated with lower scores in the physical functioning (p=<.01), role personal (p=<.01), body pain (p=<.001), general health (p=<.01), vitality (p=<.0001), social functioning (p=<.01), role emotional (p=<.01) and physical component summary (p=<.0001). Frailty was associated with an increased number of hospital visits, including inpatient (p=<.001) emergency (p=<.01) and outpatient visit(p=<.05). Frailty, depression and QoL was independent of vitamin D status.

Conclusions: Frailty in adults with CKD and DM is associated with reduced lean body mass, increased risk for depression, reduced QoL and increased risk of hospitalization, independent of vitamin D status. Rehabilitation strategies aimed at treatment of frailty in adults with CKD and DM is warranted.

Key Words: Diabetes, vitamin D, kidney, frailty, depression.

ADI Research Day, October 5, 2017
DETERMINATION OF DIETARY FIBER FERMENTATION BY THE HUMAN GUT MICROBIOTA USING A SIMPLE BATCH \textit{IN VITRO} MODEL

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\textbf{Background:} Dietary fiber consists of carbohydrates which resist the digestion from the host and therefore constitute a critical substrate for bacterial fermentation in the gastrointestinal tract. This fermentation results in the end production of Short Chain Fatty Acids (SCFAs) that are absorbed by the host and lead to numerous physiological, immunological and metabolic benefits. However, the composition and the ability of the human gut microbiome to ferment specific fiber structures is highly individualized, and little is known on how differences in fiber fermentation among individuals influence the observed health benefits. The objective of my research is to develop a simple batch \textit{in vitro} fecal fermentation (IVFF) model that mimics the fermentation in the human large intestine to determine how chemically distinct fibers are fermented by the gut microbiome and to assess the interindividual response to dietary fiber fermentation.

\textbf{Methods:} Due to the purity of four fibers (Resistant starch type 4, Acacia gum, Arabinoxylan and Microcrystalline cellulose), they were digested first. The in vitro digestion was designed to mimic the human digestion process from oral stage to small intestine stage. Batch IVFF was then carried out to quantify SCFAs produced when the digested fibers were fermented by the fecal microbiota of the participant. The fermentation was carried out in anaerobic condition at 37 °C. After 14 hours’ fermentation, fecal slurries were centrifuged at 20,000xg for 20mins, with the supernatant being analyzed for SCFA by Gas Chromatography.

\textbf{Results:} The IVFF assay could clearly illustrate the high interindividual variation that exist and show how chemically distinct fibers are fermented to SCFAs.

\textbf{Conclusions:} A simple and inexpensive IVFF system have been established that allows the determination of fiber fermentation of individual fecal samples in high throughput.

\textbf{Key words:} Dietary fiber, Gut microbiome, Short Chain Fatty Acids, \textit{In vitro} fermentation
FACTORS PREDICTING PNEUMOCOCCAL VACCINATION IN A COHORT OF 2040 ALBERTANS WITH TYPE 2 DIABETES

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Background: Guidelines recommend pneumococcal vaccination for people with diabetes because they are at high risk of morbidity (e.g. severe pneumonia, meningitis) and mortality from this infection. Although we know vaccine uptake is not ideal, reasons behind the low rate are unknown.

Methods: We examined data from the Alberta Caring for Diabetes cohort, which included socioeconomic characteristics, self-management activities, clinical monitoring activities, co-morbidities, health status measures, and health service utilization. Multivariable logistic regression analyses were conducted to identify factors associated with self-reported pneumococcal vaccination status.

Results: Mean age of the 2,040 participants was 64.4 (±11) years, 45% were women, mean duration of diabetes was 12 (±10) years, and 1,090 (53%) reported receiving a pneumococcal vaccine. Pneumococcal vaccination rates were strongly related to the number of indications (age ≥65 years, chronic [diabetes, cardiovascular, pulmonary, renal] disease, cancer, smoking, and excessive alcohol use: Figure). After multivariable analysis, age ≥65 years (adjusted odds ratio (aOR) 2.38; 95% CI 1.82-3.11), pulmonary disease (aOR 1.41; 95% CI 1.08-1.84), and cancer (aOR 1.43; 95% CI 1.06-1.93) were independently associated with vaccination. In addition to these factors, women (aOR 1.41; 95% CI 1.14-1.76) and retirees (aOR 1.39; 95% CI 1.09-1.78) were more likely to have been vaccinated.

Conclusion: This information will help shape future programs aimed at improving pneumococcal vaccine uptake in people with diabetes.

Key words: Pneumococcal Vaccination, Type 2 diabetes, Predictors.

ADI Research Day, October 5, 2017
KETONE BODIES CAN PROVIDE ADDITIONAL ENERGY FOR THE DIABETIC FAILING HEART WITHOUT COMPROMISING CARDIAC EFFICIENCY

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BACKGROUND: With global excitement surrounding the class effect of SGLT2 inhibitors improving cardiovascular outcomes, it remains enticingly unclear how the anti-hyperglycemic agent, empagliflozin, confers its cardiovascular benefits to the diabetic heart. In addition to decreasing blood glucose levels, empagliflozin also increases circulating levels of ketones in the blood. Therefore, one proposed explanation for empagliflozin’s ambiguous cardioprotection is through optimizing cardiac energy metabolism and deferring the heart’s substrate preference from fatty acids and glucose, to the “thrifty” (or efficient) ketones. However, it remains unclear whether an increase in myocardial ketone usage is beneficial for the diabetic heart. Consequently, the aim of our study was to assess the metabolic profile and cardiac efficiency of the diabetic heart in response to ketones [%-hydroxybutyrate (%OHB)]. This will help elucidate whether ketones can improve cardiac efficiency and function.

METHODS: Diabetic (db/db) 23-week-old male mice were used to characterize the metabolic profile of the diabetic heart in response to an increase in the availability of ketones. C57BL/6J mice were used as our controls. Isolated working hearts from these mice were perfused for 60 minutes with 3H or 14C labelled glucose (5mM), palmitate (0.8mM), and %OHB (0mM or 0.6mM) to assess glycolysis rates, and ketone body, fatty acid and glucose oxidation rates, with 100U/mL insulin added 30 minutes into perfusion. The pulmonary artery was also cannulated during these isolated working heart perfusions, which allowed us to quantify myocardial oxygen consumption rates and calculate cardiac efficiency by normalizing cardiac work to oxygen consumption.

RESULTS: Relative to control, db/db hearts had decreased cardiac work and the addition of %OHB did not affect cardiac work. To add, db/db hearts with and without %OHB had similar rates of glucose oxidation, palmitate oxidation and glycolysis. However, the addition of %OHB did increase the total amount of energy (ATP) produced by the db/db hearts. Interestingly, while energy production increased, oxygen consumption rates in db/db hearts did not significantly change in the presence of ketones. As such, cardiac efficiency was not affected by the addition of ketones.

CONCLUSION: The cardiac work, metabolic profile and oxygen consumption of the diabetic heart did not significantly change when supplied with ketones. However, ketones can provide additional energy to the diabetic heart without affecting cardiac efficiency. As such, ketones are not a more or less efficient fuel substrate for the diabetic heart but can still be used to increase total energy production.

KEYWORDS: ketones, cardiovascular, metabolism

ADI Research Day, October 5, 2017
INVESTIGATING THE EFFECTS OF 2-AMINOADIPIC ACID ON HUMAN ISLET FUNCTION

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Background: 2-amino adipic acid (2-AAA) is a breakdown product of lysine metabolism that has been found to be an accurate biomarker for future development of diabetes. In vivo mouse models and in vitro murine and human islet culture studies suggest that 2-AAA increases insulin release at low glucose levels. Considering previous 2-AAA studies indicating 2-AAA's glial toxicity, it is possible that 2-AAA could be modifying glutamate and cystine transport into β-cells, as the same transporters are present on both cell types. Reduction in intracellular glutamate and cystine levels could lead to reduced intracellular glutathione levels resulting in a lowered antioxidant capacity. This, along with chronically high insulin production at low glucose levels, could result in β-cell damage leading to higher incidence of future diabetes. Changes in glutathione due to 2-AAA may also affect insulin release, as modification of intracellular glutathione levels in β-cells has been found to modulate the release of insulin by affecting the activity of deSUMOylation enzymes. This research will focus on investigating 2-AAA's effects on human β-cell insulin release, glutamate and cystine transport, and glutathione production.

Methods: Dynamic glucose stimulated insulin secretion at 2.5mM low glucose followed by 11.1mM high glucose was measured by perifusing human islets with buffer containing 30μM 2-AAA at a flow rate of 250μL/min. Additional perifusion experiments included normal blood levels of glutamate and cystine in the buffer solution to better examine 2-AAA's effect on glutamate transporters. Further studies will include measurement of 2-AAA's effect on glutathione production and cell death in both the INS-1 rat β-cell line and human islets cultured overnight. These overnight cultures will include treatment with reactive oxygen species to investigate the cell's antioxidant capacity.

Results: Preliminary data suggests that adding 2-AAA to the buffer solution during perifusion, decreases the insulin response of human islets to high glucose. This was also seen when cystine and glutamate were added to the buffer solution. When these additional amino acids were added to the buffer solution, increased insulin release at low glucose was also seen.

Conclusions: Initial results from this study indicate that 2-AAA seems to be detrimental to proper insulin release at both low and high glucose. While static glucose stimulated insulin release experiments have previously found that 2-AAA increased insulin release at low glucose, these perifusion experiments indicate that insulin release is also decreased at high glucose. The next step in this study will be examining 2-AAA's effect on β-cell glutathione production and survival, to determine part of the mechanism behind 2-AAA effect on insulin release and β-cell health.

Keywords: Human Islets, 2-Amino adipic Acid, Perifusion

ADI Research Day, October 5, 2017
Scaling Up Microtissue Production

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Background: There is a growing recognition that three dimensional microtissues can provide greater physiological relevance over conventional adherent culture conditions for some applications, and their use is increasing in a number of areas including cell production/differentiation and tissue engineering. In particular, centrifugal forced aggregation in microwells yields consistent and size controlled microtissues which may be an alternative the size variant native islets used in islet transplantation procedures. The use of the microwells to generate aggregated ‘pseudo-islet’ requires scaling up the microwell system to generate a clinically relevant numbers to be used in clinical applications. The microwell bioreactor developed in this project will provide a one step method of scaling up from high throughput well plate studies.

Methods: To maintain growth conditions from a wellplate to a bioreactor, oxygen and nutrient supply were investigated. In the bioreactor, oxygen diffuses through microwell-membranes directly to the cell grown above. Oxygen diffusion was quantified by measuring transient diffusion of oxygen through the membranes and the diffusion constant was determined using ficks law. Multiple membrane material were tested. Nutrient supply was evaluated by using a batch media change method of bioreactor layers where the resident time was evaluated. Resident time was determined using a pulse input of a tracer, Methylyene Blue, whose outlet concentration was monitored using absorbance. Both empirical tests were modeled in ANSYS Fluent and the results of the experiment were compared with the simulation. Aggregation protocols of INS1 cells were used to confirm the preservation of performance between the well plates and the bioreactor.

Results: A prototype bioreactor was generated. Diffusion constants of polymer films were found to resemble literature values with an increase in diffusivity after Microwells were embossed on the surface. Optimization of the microwell layer geometry to improve the resident time is ongoing. Aggregation protocol testing is also ongoing.

Conclusion: The use of a microwell well-plates provides a high throughput platform to test aggregate performance and generation however scaling up these protocols may require further optimization and testing. The microwell bioreactor provides an immediate solution to scaling up microtissue production to clinically relevant number while maintaining existing protocols.

Key Words: bioreactor, oxygen diffusion, islet transplantation

ADI Research Day, October 5, 2017
CD4 T cells, foreign protein and CD22 control antibody response to non-self blood group A-antigen in mice

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Background: ABO-incompatible heart transplantation (ABOi-HTx) is safe during infancy and allows increased donor access. B-cell tolerance develops to donor A/B-antigen(s) (Ag) after ABOi-HTx by mechanisms remaining unclear. We developed transgenic mice (A-Tg) constitutively expressing human A-Ag on vascular endothelium and erythrocytes (RBC) to study anti-A antibody responses. CD22 participates in B-cell tolerance and we found that B cells express high-levels of CD22 in human B cells, decreasing with age. Here we used a mouse model to study the anti-A response in the context of MHC syngeneic, allogeneic and xenogeneic stimulation, and the impact of CD22 expression.

Methods: Part I: Adult wild-type (WT) C57BL/6 (B6/H-2b), BALB/c (BALB/H-2d), C3H/He (C3H/H-2k), or CD22-deficient B6 (CD22KO) mice received intraperitoneal injections of B6 or BALB A-Tg blood cells or human-RBC membranes (100ul/10%/v/v) from blood group-A (hu-A) or O (hu-O); or A-incompatible heart allografts. Serum anti-A Ab was measured by hemagglutination and ELISA (IgG and IgM); graft survival was assessed by palpation. Part II: a) To assess requirement of foreign protein to stimulate anti-A, hu-O RBC/syngeneic A-Tg cells or allogeneic A-Tg blood were co-injected in WT mice; b) to assess T cell dependence of anti-A response, CD4+ T cells were depleted from WT B6 mice before hu-A RBC injection. Part III: To assess the role of CD22, A-Tg or hu-A-RBC, were injected into CD22KO mice with or without CD4+ T-cell depletion.

Results: Part I: Exposure to allogeneic A-Tg blood cells/heart graft or xenogeneic hu-RBC induced anti-A production (Table), whereas syngeneic A-Tg blood cells did not. Part II: a) mixture of syngeneic A-Tg/hu-O RBC did not induce anti-A; b) after CD4+ T-cell depletion, hu A-RBC failed to elicit anti-A. Part III: Hu A-RBC induced a very high anti-A in CD22KO mice compared to WT B6. In contrast to WT B6 mice, anti-A Ab was elicited in CD22KO mice following injection with A-Tg blood cells or hu-A-RBC with CD4+ T cell depletion.

Conclusions: Our results show that in WT mice, anti-A antibody production depends not only on exposure to A-antigen but also co-engagement with foreign protein and a requirement for CD4+ cells; consistent with a T-dependent anti-A response. Conversely, in CD22KO mice there was no requirement for foreign protein or CD4+ cells to elicit an anti-A antibody response; consistent with a T-independent anti-A response. These findings suggest an important role for the regulatory CD22 receptor in the B cell response to ABH antigens.
THE EFFECT OF DIETARY SUPPLEMENTATION OF CHOLINE, BETAINE AND TRIMETHYLAMINE N-OXIDE ON ATHEROSCLEROSIS IN LDL RECEPTOR AND APOE KNOCK OUT MICE.

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Background: Choline is an essential nutrient that is required cell membranes, lipoprotein secretion and methyl-group metabolism. Recently it has been proposed that an excess intake of choline is converted to trimethylamine (TMA) by gut microbiota; TMA is then oxidized to trimethylamine N-oxide (TMAO) by the liver enzyme, flavin-containing monooxygenase-3. It has been hypothesized that high TMAO levels in plasma may be a biomarker for cardiovascular disease. Epidemiological studies have been shown inconsistent results about this association. Experiments where Apoe⁻/⁻ mice were fed at high choline diet showed higher TMAO plasma levels and atherosclerotic size lesion compared to controls. The aim of this study was to determine the dietary relationship between choline, and/ its metabolites, and atherosclerosis in two different atherogenic, Ldlr⁻/⁻ and Apoe⁻/⁻, mouse models.

Methods: Ldlr⁻/⁻ male mice, aged 8-10 weeks, were fed with high-fat diet (HFD: 40% of calories and 0.5% of cholesterol) for 16 weeks. In the first set of experiments, mice (N=10-12/group) were randomized to one of three dietary groups: control (0.1% choline and 0% betaine wt/wt), choline-supplemented (1% choline and 0% betaine wt/wt), or betaine-supplemented (0.1% choline and 0.9% betaine wt/wt). In the second feeding trial, mice (N=7-8/group) were randomized to one of two dietary groups: control (0% TMAO wt/wt) or TMAO-supplemented (0.2% TMAO wt/wt). Meanwhile, Apoe⁻/⁻ male mice, aged 8 weeks, were randomized to one of four dietary groups for 12 weeks: control (0.1% choline, 0% betaine and 0% TMAO wt/wt), choline-supplemented (1% choline 0% betaine and 0% TMAO wt/wt), betaine-supplemented (0.1% choline and 0.9% betaine and 0% TMAO wt/wt) or TMAO supplemented (0.1% choline, 0% betaine and 0.12% TMAO wt/wt). After the dietary intervention, the animals were euthanized, and tissues and blood collected. Aortic atherosclerotic plaque area, plasma choline and lipid metabolites were quantified. Liver histology and lipids were analyzed.

Results: In Ldlr⁻/⁻ mice, dietary supplementation with choline or TMAO increased plasma TMAO levels by 2.4- and 2-fold, respectively. Dietary betaine supplementation did not influence plasma TMAO levels. Despite the increase in plasma TMAO levels, dietary intervention did not alter atherosclerosis in either mouse model.

Conclusion: Our data suggests that the increase of TMAO levels following choline and TMAO supplementation does not influence atherosclerosis development. (Supported by CONACYT Mexico, NSERC and ALMA)

Keywords: Choline, TMAO, Atherosclerosis, Ldlr⁻/⁻ mice, Apoe⁻/⁻ mice.

ADI Research Day, October 5, 2017
**Fasting and postprandial glucose, insulin and GLP-1 levels in children with Prader-Willi Syndrome**

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**Background:** Prader-Willi Syndrome (PWS) is a unique clinical model of severe childhood obesity with increased insulin sensitivity. The incretin hormone, glucagon-like peptide 1 (GLP-1), has potent effects to stimulate insulin secretion in response to glucose; however, it is not clear if GLP-1 levels are altered in children with PWS. Therefore, the purpose of our study was to compare fasting and acute postprandial concentrations of glucose, insulin and GLP-1 in children with and without PWS.

**Methods:** Ten children with PWS and seven controls completed three separate study visits. A fasting blood sample and anthropometric measurements were completed at each study visit. Participants consumed one of the following breakfast meals at each visit: standard (350kcal, 55%CHO, 30%fat, 15%PRO), higher protein/lower carbohydrate (350kcal, 40%CHO, 30%fat, 30%PRO), higher protein/lower fat (350kcal, 55%CHO, 15%fat, 30%PRO). Blood samples were taken at 60-minute intervals for 3 hours after the meal.

**Results:** PWS and controls were of similar age and BMI-z score. PWS had lower fasting levels of glucose (p=0.033) and showed a trend (although not significant) for lower insulin and HOMA (p=0.055 for both) at baseline. Fasting GLP-1 levels in PWS children were comparable to controls. Fasting and AUC values of GLP-1 were not correlated with glucose and insulin. Glucose concentration increased over time in the PWS group (p=0.031) but not in the controls. However, insulin and GLP-1 concentration increased over time in both PWS (p<0.0005 and p=0.001) and control groups (p=0.003 and p=0.013). Postprandial absolute glucose and insulin levels were higher in the PWS group compared to the control group at three hours (p=0.003 and p=0.005, respectively) following the meal. PWS had higher glucose relative to fasting at 3 hours and higher insulin relative to fasting at 1, 2, and 3 hours compared to controls. Glucose, insulin and GLP-1 AUC were not different between meals in the control group. However, insulin AUC was higher in response to the higher protein/lower fat meal than the higher protein/lower carbohydrate meal in the PWS group only (p=0.048).

**Conclusion:** This study indicates that fasting glucose is lower while insulin and HOMA trend to be lower in PWS, suggesting that PWS children are more insulin sensitive than controls. Fasting GLP-1 levels were comparable in PWS and control children, suggesting that it is not the primary driver of insulin sensitivity in PWS. The prolonged insulin and glucose response in PWS are suggestive of lower tissue uptake due to lower muscle mass.

**Key words:** Childhood Obesity, Diet, Prader-Willi Syndrome
EXTRACELLULAR REDOX SENSITIVITY OF Kv1.2 POTASSIUM CHANNELS

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Background: The hyperglycemia and excess production of oxidative species in diabetes play an important role in its progression and in the damage of many organ systems including the nervous and cardiovascular systems. One of our objectives was to examine how the redox environment can alter the function of voltage gated potassium (Kv) channels in the central nervous system. We have discovered that a neuronal Kv channel important in regulating excitability, Kv1.2, is highly sensitive to the external redox environment. Kv1.2 channels are subject to a regulatory mechanism referred to as 'use-dependent activation' that allows channels to progressively increase activity during trains of stimuli. We hypothesize that the redox sensitivity of this channel is due to an extrinsic binding partner that modulates use-dependent activation of Kv1.2 in a redox-sensitive manner.

Methods: Kv1.2 currents and the effects of various reducing agents are measured using whole cell patch clamp electrophysiology.

Results: In this study, we demonstrate that use-dependent activation of Kv1.2 channel complexes is strongly regulated by a variety of exogenous and physiological redox species. Under ambient redox conditions, Kv1.2 channels exhibit marked cell-to-cell variability of use-dependent activation. However, exposure to mild reducing conditions normalizes this response, such that a pronounced use-dependent phenotype is consistently observed, together with a dramatic depolarizing shift of voltage-dependent activation with a V1/2 of 51 +/- 6 mV. Mutagenesis of candidate cysteine residues in Kv1.2 did not affect redox sensitivity, therefore we hypothesize a role for an extrinsic redox-sensitive interacting partner. Using a variety of redox buffers, we demonstrate that use-dependent activation is steeply regulated by redox potentials between -50 and -100 mV, within the typical extracellular range. Furthermore, effects of membrane-impermeable reducing agents demonstrate that use-dependent activation is regulated by the extracellular redox state.

Conclusions: Taken together, these findings suggest that Kv1.2 is a unique transducer of the extracellular environment, and may translate altered extracellular redox conditions to changes in cellular electrical function.

ADI Research Day, October 5, 2017
GLUCOSE-ENRICHED DIET EXTENDS LONGEVITY IN DROSOPHILA MELANOGASTER

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Background: The acquisition and use of nutrients is one of the most important processes for all forms of life. The optimization of diet has obvious benefits to both health and lifespan, but an imbalance can lead to serious metabolic diseases. I used Drosophila melanogaster to investigate the mechanisms that link dietary composition to lifespan. Many of the metabolic pathways are highly conserved between flies and mammals. As well, functionally analogous metabolic organs play similar roles between flies and mammals. One of the biggest issues with nutritional research is the variance between diets used by different labs. To address this, the Partridge lab recently described a holidic diet, in which all components are defined. In this project, I used this defined holidic diet to investigate the mechanisms that link diet and longevity.

Methods: For this project, I prepared two versions of the holidic diet: an unmodified holidic diet and a glucose-enriched holidic diet. I raised wild type flies on these two diets and measured their lifespans. I also performed several assays to compare the metabolic response of flies raised on these two diets. I measured macronutrient levels through photometric assays, determined circulating sugar levels, and performed an ELISA to compare insulin levels. To compare gene expression differences between flies raised on the two diets, I performed microarray analysis. For several experiments, I used the GAL4-UAS expression system to block or activate pathways of interest in specific metabolic tissues.

Results: Flies raised on the glucose-enriched holidic diet live longer than their counterparts raised on an unmodified holidic diet. Flies raised on the glucose-enriched diet showed no difference in weight, but had higher levels of glucose, circulating sugars, and triglycerides. Insulin expression is slightly lower for both mRNA and protein levels. This suggests that these flies may live longer through reduced insulin activity; however, I found that flies with mutated insulin signalling still lived longer on the glucose-enriched diet. Microarray analysis suggested that MAPK activity might be involved. Expression of a constitutively active form of Ras in insulin-producing cells eliminated the lifespan extension of the glucose-enriched holidic diet.

Conclusion: The glucose-enriched holidic diet extends lifespan of Drosophila through a mechanism dependent on Ras activity in insulin-producing cells. This mechanism appears to be independent of canonical insulin signalling.

Key words: Longevity, Nutrition, MAPK Signalling

ADI Research Day, October 5, 2017
METFORMIN IMPROVES GLUCOSE TOLERANCE IN YOUNG (PRE-DIABETIC) NILE RATS: AN NOVEL MODEL FOR TYPE 2 DIABETES

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Background: Nile rat (NR), a newly discovered model of spontaneous T2D, develops diabetes when fed with standard chow diet. We have reported a staged progression of T2D in NR, similar to human diabetes, with early onset of insulin resistance and prediabetes at 2 months and late onset of hyperglycemia at 12 months. However, the underlying mechanism of T2D in NR is not elucidated. Metformin (MET) is an insulin sensitizer, which has been used clinically to treat human T2D for decades, via reducing hepatic gluconeogenesis to increase insulin sensitivity. To explore the specific effect of insulin resistance on T2D development in NR, we hypothesize that intervention with metformin (MET) on young (prediabetes) NR will alleviate insulin resistance and thus prevent T2D development.

Methods: NR used in this study were fed with standard chow diet (fat 9.6%, fiber 3.2%) after weaning. Intraperitoneal glucose tolerance test (ipGTT) was performed on 22 animals at age 6 weeks to acquire a baseline for glucose tolerance in NR. Because of their aggressive behavior, all NR were anesthetized with isoflurane during the procedure. Animals were randomized into two groups: Chow or Chow+MET, n =11 each, with MET (20 mg/kg body weight) orally administered in drinking water for 7 weeks. Glucose tolerance of NR was assessed by ipGTT after 7 weeks of treatment and then animals were euthanized with a blood sample collected for fasting blood glucose and insulin measurements.

Results: Body weight (80.1±13.5 vs 82.8±9.3, g), fasting blood glucose (2.51±1.17 vs 2.47±0.85, mmol/L) and fasting plasma insulin concentration (4.91±5.67 vs 5.05±5.55, ng/mL) were similar between Chow and Chow+MET at 13 weeks, as well as insulin sensitivity index (ISI), HOMA-IR and HOMA-B. However, blood glucose during ipGTT in Chow+MET was significantly reduced as compared with Chow NR (p< 0.05), with no change seen in insulin secretion between groups. Interestingly, NR exhibited impaired glucose tolerance as early as 6 weeks, which was alleviated in Chow+MET after 7 week of treatment (p<0.001), whereas no age-related difference was observed in Chow group.

Conclusion: These finding suggest that impaired glucose tolerance occurred as early as 6 week in NR, which is alleviated by MET intervention. However, the high circulating insulin observed in Chow +MET group indicates MET alone doesn't completely block the development of prediabetes in NR. 

Key words: Nile rats, type 2 diabetes, metformin, insulin resistance

ADI Research Day, October 5, 2017
INTESTINE-SPECIFIC DELETION OF CTα PROTECTS AGAINST HIGH FAT DIET-INDUCED OBESITY

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Background: Our lab has previously reported that inhibiting de novo phosphatidylcholine (PC) synthesis via the deletion of the hepatic enzyme phosphatidylethanolamine-N-methyltransferase, protects mice from diet-induced obesity and insulin resistance; however, these mice develop liver steatosis. PC can also be produced from dietary choline by the CDP-choline pathway in all cells, and the enzyme CTP:phosphocholine Cytidylyltransferase α (CTα) regulates flux through the pathway. Our hypothesis is that inhibiting CTα specifically in the intestine will delay lipid absorption and improve indices of the metabolic syndrome.

Methods: Experiments were conducted in the setting of either a chow diet or 40% kilocalories fat diet. Blood and intestinal tissue was collected for lipid, transcriptional, protein and histological analysis. Intestinal lipid absorption was assessed by measuring triglycerides in plasma at various time-points after an olive oil challenge or after a meal.

Results: Chow-fed iCTα−/− mice have normal body weight, plasma lipids and blood glucose concentrations. When placed on a 40% high fat diet for 7 weeks, iCTα−/− mice have reduced weight gain, adiposity and fasting blood glucose concentrations as compared to controls. Studies examining the mechanisms behind this resistance to weight gain revealed that iCTα−/− mice have impaired dietary fatty acid absorption. Furthermore, iCTα−/− mice have enhanced postprandial secretion of gut hormones including GLP-1 and PYY.

Conclusion: These results provide evidence of a novel link between intestinal PC synthesis, enteroendocrine hormone secretion and whole-body energy balance.

Keywords: lipids, metabolism, intestine.

ADI Research Day, October 5, 2017
A REDUCED INTENSITY CONDITIONING PROTOCOL INDUCES TRANSIENT CHIMERICISM AND TRANSPLANT TOLERANCE TO FULLY ALLOGENEIC ISLETS IN AUTOIMMUNE DIABETIC NOD MICE

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**Background:** Allogeneic islet transplantation has the capability to restore normal glycemia in Type 1 Diabetic recipients. However, foreign islets would be rejected due to auto and alloimmune response towards pancreatic beta cells. To date, only a handful of methods were able to prolong the acceptance of allogeneic islets in tolerance resistant, non-obese diabetic (NOD) mice that had already become diabetic. Mixed chimerism via hematopoietic stem cell transplant is a robust method for generating donor specific tolerance with the potential to allow islet transplant tolerance. However, its clinical application is prevented by the toxicity of current recipient conditioning regimens. We previously showed that a T cell depletion based mixed chimerism protocol in pre-diabetic NOD mice is achievable without antibodies to CD40L (known to cause thromboembolism in humans), irradiation, or rapamycin. As generating chimerism in diabetic NOD mice is even more challenging compared to pre-diabetic ones, we sought to test if we could induce chimerism and transplant tolerance to allogeneic islets in spontaneously diabetic NOD recipients.

**Methods:** We preconditioned spontaneously diabetic NOD mice with donor specific transfusion (DST) from fully mismatched FVB mice (d-10), cyclophosphamide (d-8), antibodies against CD4/8/90 (d-6, -1, 4, 9, 14), and busulfan (d-1). Donor islets and/or bone marrow transplantation (BMT) were done at d0. Blood glucose levels of recipient mice were assessed twice weekly. Flow cytometry was used to detect chimerism.

**Results:** By using this protocol, we induced transient mixed chimerism in 6/8 diabetic NOD mice. Although chimerism in the diabetic recipient was less stable compared to pre-diabetic NOD mice, with lower chimerism levels at the early time points (d4/9/14/28) post-BMT, islet recipients (3/3) with high-level chimerism at d28 were able to maintain normal blood glucose even after donor bone marrow was rejected (2/2). Moreover, chimerism levels at d28 post-BMT were higher in recipients with an islet graft. Recipient T cells in diabetic NOD mice were depleted as efficiently as in pre-diabetic NOD mice but rebounded quickly, starting at d14, which might be associated with the instability of chimerism.

**Conclusion:** A T cell depletion based mixed chimerism protocol induces chimerism in diabetic NOD mice and promotes tolerance to fully allogeneic islets.

**Key words:** Hematopoietic chimerism, Transplantation tolerance, Bone marrow transplantation, Islet transplantation

ADI Research Day, October 5, 2017
THE LACK OF PHOSPHATIDYLETHANOLAMINE N-METHYLTRANSFERASE CAUSES HIGH-FAT DIET-INDUCED CHOLESTASIS

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**Background:** Phosphatidylethanolamine N-Methyltransferase (PEMT) is a membrane protein that catalyzes ~30% of hepatic phosphatidylcholine (PC) biosynthesis. When Pemt⁻/⁻ mice are fed a high fat diet (HFD), they are protected from diet-induced obesity and insulin resistance but develop steatohepatitis. PC is critical for maintaining membrane integrity but is also secreted into bile in relatively large quantities. Bile acids are necessary for intestinal lipid absorption. Recently, bile acids have also been identified as signaling molecules that affect metabolism and insulin sensitivity. Interestingly, PEMT has been found to be expressed in close proximity to the canalicular membrane. We hypothesize that PEMT-derived PC synthesis is critical for a properly functioning canalicular membrane and for biliary secretion.

**Methods:** Pemt⁺/+ and Pemt⁻/⁻ mice were fed a chow diet, 60% HFD for 2 or 10 weeks, or a choline supplemented HFD for 10 weeks. Gallbladder cannulations were conducted in all mice to measure bile secretion. Increasing amounts of tauroursodeoxycholic acid were infused into the jugular vein to stimulate biliary secretion in mice fed a HFD for 10 weeks. This allowed us to determine maximal biliary secretion rates. The bile salt export protein (BSEP), responsible for bile acid secretion, was visualized by IHC and measured via western blotting. Electron microscopy was employed to visualize the canalicular membrane.

**Results:** After 10 weeks of HFD, biliary secretion rates of bile acids and PC were significantly lower in Pemt⁻/⁻ mice compared to Pemt⁺/+. Maximal secretion of bile acids, phospholipids, and cholesterol were also significantly decreased in Pemt⁻/⁻ mice. Concomitant to the decrease in biliary bile acid secretion, plasma bile acids were elevated from ~15 to ~100 µM in Pemt⁻/⁻ mice. Localization of BSEP to the canalicular membrane as well as total hepatic BSEP protein was decreased in Pemt⁻/⁻ mice. Visualization of the canalicular membrane showed decreased invaginations and surface area in Pemt⁻/⁻ mice compared to Pemt⁺/+ mice.

**Conclusion:** Pemt⁻/⁻ mice develop cholestasis - an impairment in bile secretion - on a HFD. This is likely due to an altered canalicular membrane structure, causing decreased levels of BSEP protein at the canalicular membrane.

**Key Words:** Bile acids, cholestasis, phospholipids

ADI Research Day, October 5, 2017
**GLYCINE PHARMACOLOGY IN PANCREATIC ISLETS**

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**Background:** Insulin, the only blood-glucose lowering hormone in the body, is secreted from pancreatic β-cells and is regulated by neuronal, nutritional, and hormonal signals. Many neurotransmitters have been documented to modulate insulin secretion and dysfunctional neurotransmitter signalling may be involved with the pathogenesis of diabetes. Glycine is an inhibitory neurotransmitter but recent metabolic studies identify glycine as a potential biomarker of type 2 diabetes (T2D) risk. A strong correlation exists between plasma glycine concentrations and insulin sensitivity, glucose disposal, and obesity. Circulating plasma glycine concentrations are inversely related to T2D risk. The mechanism for glycine's action in diabetes is unknown.

**Methods:** Human islets were isolated in the Alberta Diabetes Institute Islet Core and the Clinical Islet Laboratory at the University of Alberta from donor organs. Electrical recordings were performed on dispersed human islets from healthy donors and donors with T2D.

**Results:** mRNA analysis of glycine receptors α1 subunit reveal splice variation producing Glycine receptor α1 variant 1 and Glycine receptor α1 variant 3 (henceforth referred to as variant 1 and variant 3 respectively), where variant 1 is the full length protein while variant 3 contains a truncation on the N-terminus. Plasmids for both variant 1 and variant 3 were created and transfected into HEK cells. Variant 3 is unable to produce a current when stimulated with 300uM glycine. Molecular dynamic modeling of the receptor was employed to further study the structural differences between variant 1 and variant 3. Binding analysis demonstrated that glycine cannot bind to the binding site in variant 3. We suspect that variant 3 maybe upregulated in T2D and may explain the reduced glycine current associated with T2D and increased plasma glucose concentration.

**Conclusion:** glycine receptor mediated current is known to be reduced in islets from human donors with T2D compared to human donors without T2D. Although insulin resistance is suspected to play a role in the reduced glycine current, our evidence suggests that upregulation of a non-functional receptor variant 3 may also contribute to reduced glycine current.

**Keywords:** Glycine receptors, human pancreatic β-cells, type 2 diabetes.

ADI Research Day, October 5, 2017
A Promising Cell-based Therapy for Type I Diabetes using Re-aggregated and Optimized Pseudoislets


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Background: Islets transplantation is a promising approach to the treatment of Type I Diabetes. However, a major clinical limitation for current islet transplantation is the inefficient survival and engraftment in the immediate post-transplant period. One reason is likely that the size of the native islets is too large for sufficient oxygen and nutrition delivery in avascular condition immediately after transplant. Quantitative modeling of oxygen delivery within islets shows significant benefits to smaller islets, and consistent with this concept, smaller human islets have been reported to perform better than larger ones in a clinical setting. Based on our previous experience in microtissue formation, we hypothesize that there exists an optimal aggregate size, at which islet cell aggregates will exhibit significantly improved viability and insulin secretion capacity, due at least in part to improved oxygen transport properties. Subsequently, the optimal outcome from in vitro experiments will be validated in vivo. We hypothesize that in vitro results will be generally predictive of and consistent with in vivo survival and function.

Methods: The Aggrewell system is used to re-aggregate the native islets to form smaller pseudoislets and centrifugation is employed to accelerate aggregation and enhance viability. Re-aggregated islet cells were cultured in supplemented CMRL-1066 for 3-5 days before transplantation. TUNEL apoptosis assay, DNA content, Insulin production capacity have been tested in Glucose Stimulated Insulin Secretion (GSIS) assay at multiple time points pre-transplantation. Native islets and pseudoislets have then been transplanted into STZ-induced diabetic Rag1 KO mice under the kidney capsule. During the 60-day post-transplant period, Blood glucose has been monitored regularly at 3 times per week, with IPGTT tested before nephrectomy. Harvested graft have assayed immunohistochemically for endocrine cell subtype portions and vessel distribution.

Results: We successfully re-aggregated the native islet cells to formed pseudoislets in our centrifugation-aided microwell system by using human donor islets. The direct comparison showed that the pseudoislets significantly outperformed the native islets after 48-hour incubation, reproducibly exhibiting a 2.9-fold increase in terms of insulin secretion per input cell basis (p<0.05). Through in vitro culture we have discovered a better oxygen access and maintained significantly lower apoptosis level among pseudoislets. In full mass transplantation, pseudoislets restored normglycemia within 1st week post-transplantation. And at 500 IEQ marginal mass transplantation level, the proportion of mice restored euglycemia in pseudoislets group is seemed to be improved over native islets group and with improved glucose clearance profile. Further quantitative analyses of islet graft have suggested interesting similarities and differences in terms of graft composition and vessel distribution.

Conclusion: Overall the new approach to the generation of pseudoislets is feasible. This novel approach of generating size-controlled pseudoislets have substantially improved efficiency compared to conventional spontaneous aggregation or hanging drop method. Pseudoislets generated in this system have showed enhanced effectiveness and function both in vitro and in vivo compared to unmodified native islets. By further systematically optimizing the bio-process of pseudoislets formation, we will continue enhancing both the availability and performance of pseudoislets that could be rapidly applied to boost the effectiveness of current islet transplantation. The results of this project will yield a substantial improvement in the consistency and efficacy of islet cell preparations for transplantation; and lay a foundation for rapid transition to the clinic, resulting in significant advances in human health through the treatment of insulin-dependent diabetes.

Keywords: Pseudoislets, Type I diabetes, Micro-tissue engineering, Marginal mass transplantation
PRE-PREGNANCY DIETARY PATTERNS AND ASSOCIATIONS WITH SOCIO-DEMOGRAPHIC CHARACTERISTICS AND MATERNAL GESTATIONAL WEIGHT GAIN

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Background Few studies have explored diet prior to pregnancy and its relationship with pregnancy outcomes. The objectives of this study were to: (i) derive pre-pregnancy dietary patterns for women enrolled in a prospective cohort (APrON) in Alberta and describe associations between diet patterns with socio-demographics and gestational weight gain.

Methods Upon enrollment into the APrON study, women (n=1545) completed a 142-item food frequency questionnaire (FFQ) to assess frequency of foods and beverages consumed ‘prior to pregnancy’. Dietary patterns were derived using principal components analysis. Scores were calculated to represent women's compliance with each dietary pattern retained. These scores were expressed as z-scores.

Results Four patterns were retained which, combined, accounted for 22.9% of the variation in diet. The four patterns were termed a ‘Healthy Eating’, ‘Meat and Refined Carbohydrate’, ‘Beans, Cheese and Salad’ and ‘Tea and Coffee’, based on the foods which characterized the patterns. Higher 'Healthy Eating' scores were more likely to be seen in those with higher levels of education (β=0.13; P<0.001), white Caucasian ethnicity (β=0.45; P<0.001), whereas women who were obese were less likely than women with a normal BMI to have higher healthy eating scores (β=-0.21; P=0.025). Women with higher ‘Meat and Refined Carbohydrate' scores were more likely to be white Caucasian ethnicity (β=-0.55; P<0.001) or have lower levels of education (β=-0.06; P=0.021). Women with higher ‘Beans, Cheese and Salad' scores were more likely to have higher household incomes (β=0.07; P=0.04) or be non-white Caucasian ethnicity (β=-0.42; P<0.001). Women with higher ‘Tea and Coffee' pattern scores were more likely to exceed GWG guidelines (RRR 1.14; P=0.04), independent of pre-pregnancy BMI and education.

Conclusion Our observation that women with higher ‘Tea and Coffee' pattern scores were more likely to exceed GWG guidelines, requires further examination. A better understanding of whether this pattern of diet represents a type of lifestyle or behavior which could contribute to excess gestational weight gain is needed to identify appropriate strategies for intervention.

Key words: Pre-pregnancy diet, patterns analysis, gestational weight gain
PERSONALIZING OBESITY MANAGEMENT IN PRIMARY CARE: PATIENT EXPERIENCE AND SELF-MANAGEMENT OUTCOMES

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Background: Obesity is a complex, chronic disease, significantly associated with diabetes. Clinical consultation approaches in primary care have not been effective in obesity prevention and management. To address this, it is essential to understand how consultations can be personalized to maximize impact on patients’ everyday efforts to improve health. Integrating the 5As of Obesity Management with Collaborative Deliberation to develop an approach, this study examines how patients perceive interpersonal work, communication, and content; and how this impacts self-management as a result. In collaboration with PCN clinicians and patients, this project uses in-depth qualitative methods to identify key elements of personalized obesity assessment and care planning and appropriate patient outcomes to inform a future trial.

Methods: 20 patients with obesity purposefully sampled for diversity to reflect the population seeking primary care support with weight management. Video-recorded consultations followed by semi-structured patient and clinician interviews. Documentation of impact on everyday self-management through diaries and two follow-up interviews over 6-10 weeks. Data is managed and coded in NVIVO 11. A code manual was established through iterative inductive and deductive cross-coding and inter-coder agreement. Identification of themes was guided by both a pragmatic clinical perspective and dialogical interaction analysis.

Results: Three themes appear central to achieving a personalized and impactful consultation from the patient perspective: (1) patient story of their weight was central for anchoring assessment and care planning; (2) collaborative deliberation about root causes, challenges, strengths, preferences, and barriers resulted in shared conception of the condition and shared decisions about care priorities and strategies that fit patient context; (3) approach shifted patients toward realistic expectations, increased self-efficacy, and increased awareness of how life context, emotions, and weight interact. These interpersonal processes underpinned consultation techniques and were decisive for patient activation and successes with implementing their care plan.

Conclusions: Collaborative, personalized obesity consultations are key in supporting patient self-efficacy and self-care and foundational for optimizing interdisciplinary clinical care to improve health outcomes.

Keywords: primary care, obesity management, person-focused care, patient experience

ADI Research Day, October 5, 2017
PRE-PREGNANCY DIETARY PATTERNS AND PREGNANCY COMPLICATIONS

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Background: There is a paucity of evidence relating diet prior to pregnancy and complications in pregnancy. Deriving dietary patterns allows for the examination of the entire diet as opposed to single nutrient/food analysis. The aim of this study was to explore the relationship between pre-pregnancy dietary patterns and pregnancy complications including gestational diabetes, gestational hypertension and large or small for gestational age.

Methods: Pre-pregnancy dietary patterns were derived from data collected in the APrON study. Women (n=1545) completed a 142-item food frequency questionnaire reflecting diet in the year prior to pregnancy. Dietary patterns we derived using principle components analysis. Using logistic regression, associations between dietary patterns and pregnancy complications (gestational diabetes, gestational hypertension, large for gestational age, small for gestational age) were tested. Covariates included energy intake, age, ethnicity, income, education, marital status, work, leisure activity and pre-pregnancy body mass index (BMI).

Results: Four dietary patterns namely “healthy eating, “meat and refined carbohydrate”, “beans, cheese and salads”, and “tea and coffee” were derived, representing 22.9% of the variance in diet. The “healthy eating” pattern was inversely associated with gestational hypertension ($\beta$ 0.56 (95% CI -0.41, -0.03) p=0.005 and not associated with other complications. The Healthy Pattern was characterized by vegetables (green, orange and other), fruit (excluding juice), oils, brown pasta/rice, fish and dried fruit. The “meat and refined carbohydrates”, “beans, cheese and salad”, and “tea and coffee” patterns were not associated with any pregnancy complications.

Conclusion: This is the first study to investigate pre-pregnancy dietary patterns in relation to pregnancy complications in Alberta. Women with higher pre-pregnancy “healthy eating” scores were less likely to have gestational hypertension. These findings may suggest a protective effect of healthy pre-pregnancy diet on gestational hypertension.

Keywords: Pre-pregnancy diet, dietary patterns, complications, gestational hypertension
POST-TRANSPLANT CHARACTERIZATION OF LONG-TERM FUNCTIONAL HESC-DERIVED PANCREATIC ENDODERM GRAFTS

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Background: Beta cell replacement therapy is an effective means to restore glucose homeostasis in a subset of individuals with type 1 diabetes. The scarcity of human donor pancreata further restricts the expansive application of this therapy. Insulin producing cells derived from human embryonic cells (hESC), have been developed in vitro. However, translation to clinical investigation and long-term graft analysis has been limited. Herein, we examine the long-term efficacy of hESC derived pancreatic endoderm (PE) cells to maintain recipient normoglycemic post-transplant and characterize the PE grafts for cell differentiation and neoplasm.

Methods: Subsequent to a month catheter implantation period, chemically induced diabetic immune deficient mice were transplanted with 0.5-1.0 x 10^7 cells of PE cells into the subcutaneous device-less (DL) site. Post-transplant long-term function was assessed through twice-weekly non-fasting blood glucose measurements, human C-peptide secretion and intraperitoneal glucose tolerance testing (IPGTT) for 72-weeks. Explanted grafts were assessed for ex vivo function and immunohistochemically for endocrine and neoplastic markers.

Results: All recipients (n=8) of PE cells transplanted into the subcutaneous DL site maintained normoglycemia until their grafts were retrieved 72-weeks post-transplant; at which they become hyperglycemic. Serum human C-peptide levels, collected 1-year post-transplant, demonstrated significant glucose-responsiveness (P<0.01, paired, two-tailed t-test). Intraperitoneal glucose tolerance test of recipients at 52-weeks and 72-weeks post-transplant did not differ (P>0.05, two-tailed unpaired t-test) and mirrored the glucose clearance profiles of non-diabetic controls. Recipients presented with ‘cyst-like’ formations, which resolved post-fine needle aspiration. Explanted grafts demonstrated similar insulin secretory capacity as human islets as assessed by perifusion. Retrieved grafts stained positive for all endocrine cells and where characterized to possess ductal hyperplastic cells.

Conclusion: This long-term characterization study of PE cells transplanted into the DL site demonstrates that these cells can differentiation in vivo into functional, glucose-responsive insulin-producing cells that restore stable glycemic control in a physiological manner. Furthermore, this study highlights the applicability of transplanting hESC-derived cells under the skin while confirming their minimal teratoma risk.

Keywords: Pancreatic endoderm cells, Human pluripotent stem cells, Transplantation

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Molecular Interactions between Kv4.3 and its Auxiliary Subunits- A Biochemical Anatomy of Idiopathic Ventricular Fibrillation

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BACKGROUND: Diabetes is one of the strongest and independent risk factor for cardiovascular disorders, often associated with atrial fibrillation (AF) and ventricular arrhythmias (VA). Our study focuses on understanding the molecular basis of idiopathic ventricular fibrillation (IVF), a lethal cardiac arrhythmia, causing 10% of sudden cardiac death. Previously we identified crucial role of DPP6, a Kv4.3-associating β subunit, in Purkinje fiber Ito and gene variants causing DPP6 gain-of-function in IVF. Little is known about the molecular basis of DPP6 interaction with the Ito α subunit Kv4.3. Our goal is to understand the role of DPP6 in the native complex of Kv4.3, consisting of the Ito α subunit Kv4.3 and its auxiliary subunits DPP6 and KChIP2.

METHODS: We developed a computational model of Kv4.3 in complex with KChIP2 and DPP6, using AutoDock Vina. The model predicted several binding interfaces between these proteins, which were verified by expressing wild type and engineered mutant subunits in HEK cells followed by current measurement by patch clamp, 48 hours after transfection.

RESULTS: WT Kv4.3 showed substantial current enhancement upon co-expression with DPP6, as previously reported. Deletion of 5 amino acids from the Kv4.3 N-terminus decreased the peak-current density compared to WT Kv4.3 but did not prevent current enhancement by DPP6, suggesting that this region is not essential for interaction with DPP6. Neutralization of a tribasic motif in Kv4.3 to alanines enhanced the DPP6-mediated Kv4.3 current increase. Deletion of the N-terminus of DPP6 prevented Kv4.3 current enhancement. Neutralization of either positively and negatively charged regions in DPP6 significantly attenuated Kv4.3 current enhancement. The effect of KChIP2, the other auxiliary subunit of Kv4.3 showed completely different effect from that of DPP6, when co-expressed with Kv4.3. Besides increasing the peak current density, KChIP2 also shifted the activation voltage (V50) towards more negative, compared to the wt Kv4.3 and Kv4.3-DPP6 complex. To study the nature of interaction between the three proteins, we co-expressed DPP6 and KChIP2 with Kv4.3. Our results showed that DPP6 complements the effect of KChIP2 in the ternary complex, by augmenting the current enhancement effect, caused by KChIP2 alone. We also found that unlike DPP6, Kv4.3 N-terminus (2-5aa) is important for interaction with KChIP2. Our experimental results suggest that the interaction site between KChIP2 and DPP6 is located in the N-terminal region (10-25aa) of KChIP2.

CONCLUSION: We believe that these results provide important insights into the biochemical anatomy of IVF and may help to develop effective molecularly-targeted blockers for patients with IVF-inducing DPP6 gain-of-function.

KEYWORDS: Ventricular arrhythmia, cardiovascular disease, potassium channel, electrophysiology
NOR-1, A NOVEL MEDIATOR OF CLOZAPINE-INDUCED APOPTOSIS IN PANCREATIC BETA-CELLS

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Atypical antipsychotic drugs, such as Clozapine and Olanzapine, are used for the management of schizophrenia. They show greater efficacy over conventional medications. However, due to important side effects, they are reserved for patients that are unresponsive to conventional neuroleptics. Importantly, atypical antipsychotic drugs have been associated with increased risks of diabetes, which contribute to a 3-fold increase in mortality rate among schizophrenia patients. The mechanism by which these drugs cause diabetes remains elusive.

Our previous study characterized the orphan receptor Nor1 (Nr4a3) as a potential “diabetogene”. Indeed, we have shown that Nor1 is a prominent mediator of β-cell death and that Nor1 expression is increased in pancreatic islets of diabetic patients. Reports that Clozapine could exert its antipsychotic actions by activating Nor1 in specific brain regions prompted us to test the hypothesis that Clozapine could kill β-cells via the same molecular mechanism.

Our results demonstrate that Clozapine dose-dependently induced apoptosis in both INS-1 cells and human islets. This effect was not observed with SB243213, another agent with anti-psychotic properties. We also show that genetic inhibition of Nor-1 prevented Clozapine-induced β-cell apoptosis. Our mechanistic studies indicate that Clozapine reiterated the deleterious actions of Nor-1 on mitochondrial function and fractionation.

Altogether, our results suggest that Clozapine is highly toxic for β-cells and raises the possibility that patients treated with Clozapine develop diabetes as a consequence of β-cell destruction.

Keywords: Clozapine, Nor-1, apoptosis
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