Abstract A1

Characterization of Poly(Acrylic acid)-modified CNC Based Bio-adhesive Nano-gel for Drug Delivery in Colorectal Cancer

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Purpose: Colorectal Cancer contributes to 12% of Canada's total cancer diagnoses per year. Surgery is the primary treatment option. Systemically administrated chemotherapeutic drugs are often used to treat colorectal cancer but, due to adverse effects, are not well tolerated. To limit systemic adverse effects, a muco-adhesive local drug therapy, is proposed in this work. In this study we described the development and characterization of a muco-adhesive nanogel consisting of cellulose nanocrystal (CNC) and polyacrylic acid (PAA) and their complex with cisplatin (CDDP).
Methods: Zeta-potential and dynamic light scattering (DLS) measurements were used to characterize different CNC-PAA-CDDP formulations. The *in vitro* release profile of CDDP from different CNC/PAA complexes was assessed using dialysis method and ICP-MS technique. The *in vitro* cytotoxicity of CDDP in complexation with differing CNC/PAA formulations, was evaluated in HCT 116 cells at CDDP concentrations of 1.17-600 µM for 72 h using MTT assay. The cytotoxicity of the CNC/PAA nanogel carriers without CDDP was also assessed as control.
Results: Formulations under study, formed nano-sized complexes with an average diameter in the range of 3nm-4µm as evidenced by DLS measurements. A slow release profile of CDDP complexed with CNC-PAA formulations was observed with ~ 35-50% release from differing CNC/PAA formulations compared to 80% release for CDDP alone in solution at 24 h. The extent of CDDP release from the CNC-PAA complexes was found to be dependent on the molecular weight of PAA. In line with the slow drug release profile for CNC-PAA formulated CDDP, the *in vitro* cytotoxicity evaluation showed ~ 4 times higher IC50 values compared to free drug.
Conclusion: The developed CNC-PAA nanogels can serve as a carrier for local delivery of CDDP in colorectal cancer potentially minimizing systemic drug exposure and adverse effects. The characterization of this formulation is the first step in achieving this new localized cancer treatment.

Abstract A2

Pharmaceutical Characterization and Analysis of commercially available Biologicals Hemp Products

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Purpose: The purpose of this study is to develop and validate HPLC assays to quantify different cannabinoids i.e., Cannabidavarin (CBDV), Cannabigerol (CBG), Cannabidiol (CBD), and Tetrahydrocannabivarin (THCV) in commercially available hemp products. These cannabinoids are major component found in commercial hemp products and most of the times available in unknown amounts. Here we also characterize Cannaflakes using microCT, scanning dynamic light scatter (DLS) and Transmission electron microscopy (TEM) techniques.
Methods: Cannabinoids were extracted from commercial hemp products using organic solvent methanol. Two different HPLC assay methods were developed to quantify cannabinoids. The first method used an isocratic mobile phase of acetonitrile:water (75:25) at a flow rate of 0.5 ml/min with the column oven temperature set at 30°C and the second method was developed using a gradient program (0 – 27 minutes 62% B, 27 – 55 minutes 68% B, 55 – 62 minutes 62% B. A = Water and B = Methanol) with a flowrate of

1 ml/min and column oven temperature set at 50°C. In both the methods C18 column were used and cannabinoids were detected at 210 nm wavelength. DLS was used to characterize Cannaflake by determining the particle size and distribution by intensity in different dispersion mediums (anhydrous ethanol and methanol). Furthermore, morphology were determine using microCT scanning method.
Results: Two HPLC methods were developed and validated to quantify cannabinoids. Standard curves display excellent linearity ($r^2 \geq 0.99$), from concentrations range between 1 to 50 µg/mL. The intra-day and inter-day variation were negligible. microCT scans showed the distribution of the flakes. DLS data represent homogenously distributed particles in methanol as compared to anhydrous ethanol.
Conclusions: Commercially available hemp products were quantified for their cannabinoids CBD, CBG, CBDV, and THCV using two HPLC methods developed. Furthermore, the product, Cannaflake organic extracts were characterized with DLS for particle size distribution.

Abstract A3

***In Vitro* Characterization and Muco-adhesive\retentive Properties of Novel Poly(acrylic acid) Grafted Cellulose Nanocrystal Hydrogel Films For Local Delivery of Cisplatin in Oral Cancer**

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Purpose: Oral squamous cell carcinoma (OSCC) is the most prevalent and dangerous form of oral cancer. In Canada, the 5-year survival for oral cancer is 64%. Surgery, radiation and chemotherapy are treatment options for OSCC. Systemic administration of Platinum(Pt)-based antineoplastic agents are commonly used which associate with sever nephro- and neurotoxicity. Local delivery of such agents in oral cavity can assist in providing a higher concentration of the drug at the tumor site while reducing the systemic toxicities. In this work, we evaluated the application of a novel mucoadhesive hydrogel based on poly(acrylic acid)-grafted-cellulose nanocrystal (CNC-PAA), for local delivery of cisplatin in OSCC.
Methods: The developed hydrogels were evaluated for their cytotoxicity against two human OSCC cell lines. *In vitro* release of platinum from the hydrogel films was studied via the dialysis method. Additionally, we described the designed and application of a novel apparatus used to evaluate the *ex vivo* muco-adhesive/retentive behavior of the developed hydrogel films by measuring the kinetics of gel/platinum wash-out from the surface of porcine buccal tissue by simulated saliva fluid.
Results: Our results showed a lower *in vitro* cytotoxicity for the CNC-PAA formulation of cisplatin compared to the free drug (2-3 fold increase in IC_{50}), owing to a slower drug release from this formulation. Only 25% of incorporated cisplatin was released from CNC-PAA-Pt films after 2 hr compared to > 70 % release of free cisplatin, at the same time point. The results from muco-retentive apparatus confirmed the advantage of PAA-grafted-CNC compared to PAA or CNC alone in the formation of muco-retentive hydrogels.
Conclusion: The findings demonstrated the potential applicability of the CNC-PAA as a safe and efficient nano-gel carrier for Pt-based chemotherapeutic in oral cancer therapy.
Funding: Alberta Innovates Biosolutions

Abstract A4

Nanomedicine for tumor targeted delivery of novel inhibitors of DNA repair to EGFR expressing orthotopical colorectal cancer xenografts in mice

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Purpose: Colorectal cancer (CRC) affects nearly 1.4 million people worldwide and over 60% of CRC patients will eventually relapse or develop *de novo* metastatic disease.
Methods: Our research group has previously reported on the development of an inhibitor of a DNA repair enzyme, i.e., polynucleotide kinase/phosphatase (PNKP), known as A83B4C63, and its polymer-based nanoparticle formulations as novel drugs against CRC. We have also shown that the pharmacological inhibitors and genetic silencers of PNKP to be synthetic lethal partners of a tumor suppressor protein, phosphatase and tensin homologue (PTEN), which is frequently disrupted in CRC. The aim of current study was to assess the activity of a second-generation nanoparticle formulation of A83B4C63, i.e., nanoparticles modified with epidermal growth factor (EGFR) targeting GE11 peptide on their surface (GE11-NP's), in CRC models.
Results: We, hypothesized that GE11 modified nanocarriers would provide a superior delivery of A83B4C63 to CRC, leading to improved anticancer outcome in PTEN-negative CRC models both *in vitro* and in orthotopic CRC models *in vivo*. Our data corroborated that GE11 modification on the nano-delivery system to positively impact the uptake of nanoparticles by EGFR-expressing CRC cells, without any negative impact on their physicochemical properties.
Conclusion: GE11-NP's loaded with A83B4C63 were also found to be more effective in inhibiting the growth of PTEN negative CRC tumors, when compared to the unmodified A83B4C63 formulations, leading to elongated mice survival, *in vivo*.

Abstract A5

The roles of fatty acid on physicochemical properties and improved cancer targeting of fatty acid conjugated albumin nanoparticles

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Purpose: The aim of this study was to investigate the impact of different chain length fatty acids on physicochemical properties and cancer targeting of fatty acid conjugated albumin nanoparticles (ANPs).
Methods: Two different types of fatty acids (short chain, 2-hydroxybutyric acid, C4; long chain, oleic acid, C18:1) were conjugated to albumin via simple 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDC) coupling reaction. Structural modulations of fatty acid conjugated albumin were identified by FT-IR spectroscopy, MALDI-TOF and TNBS assay. Doxorubicin HCl (DOX) was selected as model drug for verifying this system. Additionally, the structures of DOX-loaded fatty acid conjugated ANPs were characterized by Transmission electron microscopy (TEM) equipped with Energy-dispersive X-ray spectroscopy (EDS). *In vitro* cellular cytotoxicity and uptake of the DOX formulations were evaluated in three cancer cell lines (A549, PANC-1, and HT-29).
Results: Fatty acid conjugated albumin supported the formation of self-assembled structures with an average size of approximately 200 nm and negative charge, when incubated with excess DOX in an aqueous solution. DOX-loaded fatty acid conjugated ANPs allowed efficient encapsulation of hydrophobic DOX into the core of the self-assembled structure, enabling a sustained release behavior in PBS pH 7.4 medium. DOX-loaded fatty acid conjugated ANPs showed an increased cytotoxic effects *in vitro*. Specifically, *in vitro* cytotoxicity studies with three cancer cell lines (A549, HT-29, and PANC-1) indicated that DOX-loaded C18:1 conjugated ANPs have distinctive cytotoxic effects compared to

Doxil®. Confocal microscopy and flow cytometry exhibited that the cellular uptake of DOX-loaded fatty acid conjugated ANPs was varied by the different chain lengths of fatty acids.
Conclusions: This study could provide versatility of fatty acid conjugated ANPs by changing the type of fatty acids and related preparation methods in drug delivery and cancer targeting therapy.
Support: Grant# 16173MFDS142, the Ministry of Food and Drug Safety, Republic of Korea.

Abstract A6 (oral presentation, poster not judged)
A new synthetically lethal nanomedicine for colorectal cancer therapy
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Purpose: Phosphatase and TENsin homolog (PTEN) is a tumor-suppressor gene that is lost in up to 75% of aggressive colorectal cancer (CRC). The co-depletion of PTEN and a DNA repair enzyme known as polynucleotide kinase phosphatase (PNKP), has been identified to lead to synthetic lethality in several cancer cell lines including CRC cells. Our aim was 1) to develop novel PNKP inhibitors and their nanoparticle (NP) formulations for tumor enhanced delivery; and 2) to investigate the anticancer activity of PNKP inhibitor as free and NP formulation in wild-type ($PTEN^{+/+}$) and PTEN-deficient ($PTEN^{-/-}$) CRC xenograft in mice.
Methods: A83B4C63 was either encapsulated in methoxy poly(ethylene oxide)-b-poly(α-benzyl carboxylate-ε-caprolactone) (PEO-*b*-PBCL) NPs or solubilized with the aid of Cremophor EL: Ethanol (CE). The biodistribution of A83B4C63 for both formulations was determined in HCT116 (PTEN positive and negative) tumor xenograft bearing animals (n=4) 24 h after 3 every other day intravenous (IV) injections of 25 mg/kg. Tumor tissues were also immunostained with Ki-67 antibody. The anticancer activity of both formulations was determined in both xenografts in NIH-III nude mice (n = 8) following the same dosing schedule repeated after a one week gap for a total of 6 IV injections.
Results: A significantly higher concentration of A83B4C63 was measured in plasma, tumor, and liver when delivered by NPs compared to CE formulation in HCT116/$PTEN^{-/-}$ xenografts. The NPs of A83B4C63 reduced the rate of HCT116/$PTEN^{-/-}$ xenograft growth more efficiently than free drug. This was in contrast to wild-type xenografts, which showed similar growth rates following systemic administration of A83B4C63 in either formulation, formulation excipients (without drug) or 5% dextrose. *In vivo* anti-proliferative efficacy was observed only in PTEN-deficient tumors-bearing xenograft in mice that received the NPs of A83B4C63.
Conclusion: Delivery of A83B4C63 by PEO-*b*-PBCL NPs demonstrates a promising new monotherapeutic option in PTEN-deficient CRC.

Abstract B1 (oral presentation, poster not judged)
Development of a highly-specific analytical method for colchicine in blood fluids of rats
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Purpose: Colchicine (COL) is used in the treatment of gout. It also has the potential to block the formation of intestinal lymph. This makes it a potential candidate for a non-surgical means of blocking lymph and this examining the contribution of intestinal lymph to the absorption of fat-soluble vitamins and other

lipophilic compounds including drugs. Here we sought to develop a sensitive and specific liquid chromatographic method with mass spectrometry detection for assay of COL in rat specimens.
Methods: Extraction of COL and colchicine deuterated in the 6 position as internal standard (IS) was made from 0.1 mL blood or plasma was undertaken using n-hexane:dichloromethane:isopropanol (300:150:15, v/v/v). This was followed by vortex mixing of tubes for 30 s, shaking for 10 min and then centrifugation at 3000 g for 10 min. The organic solvent layer was transferred to new tubes, then evaporated to dryness in vacuo. The dried residues were reconstituted using 100 µL of HPLC grade methanol: water (10:90, v/v). The mobile phase, a combination of formic acid:10 mM ammonium acetate:methanol (1:49:75, v/v/v), was pumped isocratically at a flow rate of 0.5 mL/min. The detector was operated in a positive multiple reaction monitoring (MRM) mode. COL was monitored using the transition m/z 400.30 → 358.30 and for IS m/z 406.3→362.3. Compound-dependent parameters including MRM mass transitions, Q1/Q3 pre-bias and collision energy (CE) were initially optimized automatically using LabSolutions software by flow injecting a mixture of COL and IS. The compounds and instrument conditions were further optimized manually. The final optimization was associated with highest sensitivity for the most abundant product ions in Q3 MS spectra for COL and IS.
Result: The assay exhibited excellent linearity (r^2>0.999) in peak response over the concentration ranges of 0.5-40 ng/mL COL in blood fluid. The intra- and inter-batch coefficients of variation and percent error were ≤15% and the recovery was ≥96%. All exposed samples to stability test were within ±15% of the nominal concentration.
Conclusion: The method displayed high calibers of sensitivity and selectivity for detecting very low concentrations of COL in rat. The assay may be of use in arriving at dose levels that can allow COL to be used as an inhibitor of lymphatic absorption.

Abstract B2 (oral presentation, poster not judged)

19-(S/R)Hydroxyeicosatetraenoic Acid is a Novel Endogenous Inhibitor of Cytochrome P450 1B1 in Enantioselective Manner

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Purpose: CYP1B1 is known to contribute to the pathogenesis of several diseases such as cancer and cardiac hypertrophy by forming the toxic metabolites. We recently reported that the arachidonic acid metabolite, 19(S/R)hydroxyeicosatetraenoic (HETE) acid, confers cardioprotection against cardiac hypertrophy by inhibiting the formation of cardiotoxic metabolites, midchain HETEs, known to be formed by CYP1B1. This raised the question whether 19(S/R)-HETE can directly inhibit the CYP1B1.
Methods: Human ventricular cardiomyocytes, RL-14 cells were treated with vehicle or 10 µM Ang II in the absence and presence of 20 µM 19(R)-HETE or 19(S)-HETE for 24 h. Gene and protein expression were measured using real-time PCR and Western blot analysis, respectively. The level of mid-chain HETEs was determined using LC/MS. The O-dealkylation rate of 7-ethoxyresorufin (EROD) by recombinant human CYP1B1 was measured in the absence and presence of 19(R)-HETE or 19(S)-HETE.
Results: The results showed that both 19(R)-HETE and 19(S)-HETE significantly decreased the metabolite formation rate of midchain HETEs, namely 8-, 9-, 12- and 15-HETE compared to control group. Nonlinear regression analysis and comparisons showed that the mode of inhibition for 19(R)-HETE and 19(S)-HETE is non-competitive inhibition of CYP1B1 enzyme. Dixon plots showed that 19(R)-HETE and 19(S)-HETE have Ki values of 89.1 and 37.3 nM, respectively. The Ki values of both enantiomers showed that the S-enantiomer is more potent than the R-enantiomer by approximately 2.4 fold.
Conclusion: The current study suggests that 19(*R*)-HETE and 19(*S*)-HETE could be considered a novel therapeutic modality in the treatment of cardiac hypertrophy, and cancer. Moreover, given that a non-competitive inhibitor might bind to the enzyme regulatory region, 19(*R*)-HETE and 19(*S*)-HETE could be the focus for unraveling the obscure mechanisms of CYP1B1 enzymatic reaction.

Support: This work was supported by a grant from CIHR to A.O.S.E. S.M.S. is the recipient of Alberta Innovates Graduate Student Scholarship.

Abstract B3

Feasibility of using Statistical Natural Language Processing as Pharmacodynamic in Population PKPD Analysis from Clinical Trial Data.

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Purpose: This study was designed to determine the feasibility of using sentiment scoring derived from natural language processing (NLP) as pharmacodynamics data, and whether it can be linked to a pharmacokinetic model to evaluate a concentration-effect relationship.
Methods: Data was obtained from two clinical trials of voclosporin: the phase 2b PROMISE study in renal allograft patients, and the phase 3 study in plaque psoriasis. Population pharmacokinetics and pharmacokinetic-pharmacodynamic (PKPD) modeling was performed using Monolix TM (MonolixSuite2018R2,Monolix project, France). Statistics were done using R 3.6.0 (R Core Team, 2019, https://cran.r-project.org/) and the Syuzhet package 10 was applied to extract sentiment from the plaque psoriasis trial general comments. The sentiment of each sentence in the general comments was scored using the Syuzhet package and then sentiment score was used as pharmacodynamic data in the PKPD modeling.
Results: An extravascular administration model with first a order absorption (Ka) and a lag time, with a central and peripheral compartment with linear elimination was determined. Weight and group (transplant) were identified as covariates for clearance, while age was identified as a covariate for Ka. Drug concentration was plotted against the pharmacodynamics data (the Syuzhet sentiment score) to form a PKPD model. A simple Emax model was determined to have the best fit over a sigmoid Emax model.
Conclusion: This study has shown feasibility for the novel application of NLP endpoints as pharmacodynamic data sources in the application of population PKPD modeling. As well, this study has identified certain barriers that must be assessed prior to application of this novel technique in drug development and research.

Abstract B4

A Method to Isolate Novel Bone-Targeting Parathyroid Hormone Conjugates From Plasma For Pharmacokinetic Evaluation

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Objective: We have developed, synthesized and patented a direct bone-targeting variant of parathyroid hormone, by conjugation to bisphosphonate (BP) drug bone-seeking functional groups. The bisphosphonate-tethered PTH molecules are thereby able to be guided to the surfaces of bone where they interact with their specific receptors on bone cells. This drug delivery strategy addresses shortcomings with current osteoporosis treatments such as Teriparatide (recombinant PTH(1-34)), which has a short half-life (2-3mins) and reduced bioavailability of the peptide hormone to bone cells due to PTH receptors present in many non-skeletal tissues.
Methods: Fmoc solid phase scheme with lysine-13 N-Boc protection-deprotection was used to construct PTH(1-34) with a bisphosphonate residue tethered via a 27 residue PEG linkage to Lys-13 (BP-PEG27-PTH). Identity was confirmed by an AB SCIEX API 4000 LC/MS/MS system for the mass analysis and detection of BP-PEG27-PTH bone-seeking conjugate. The BP-PEG27-PTH conjugate or commercially obtained PTH(1-34) was injected into cohorts of rats (n=10) with jugular vein cannulation. Plasma samples were reacted with custom hydroxyapatite binding assays to isolate BP-conjugates by virtue of

their mineral affinity. After washing, the PEG linkage was cleaved using sodium periodate to release PTH for subsequent quantification by ELISA.
Results: A combination of micro-BCA, ELISA and HPLC analysis were used to confirm successful cleavage of the PEG linker with no degradation effect on PTH. Intact PTH(1-34) allows for accurate and reliable detection of PTH using ELISA. We have begun the process of PTH quantification using ELISA and subsequent pharmacokinetic evaluation will follow to determine biodistribution, clearance, and retention of BP-PEG27-PTH to correlate serum concentration with pharmacological response.
Conclusions: Our bone-targeting formulation of bisphosphonate-tethered PTH represents a novel class of bone-targeting biologic drugs. This new compound offers enormous promise in the reduction of serious side-effects experienced with current bone drugs and improved treatments for bone disease.
Support: CGS-M CIHR

Abstract C1

Skeletal muscle ketone body oxidation as a novel target for improving obesity–induced dysglycemia in mice

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Purpose: Obesity is a major risk factor for dysglycemia and type 2 diabetes (T2D). Despite well-characterized perturbations in carbohydrate/lipid/amino acid metabolism contributing to obesity-induced T2D, it remains unknown whether ketone body metabolism is perturbed in obesity/T2D. Hence, our goal was to characterize and determine whether alterations in ketone body metabolism influence T2D pathology.
Methods: Eight-week-old C57BL/6J mice, or skeletal muscle-specific succinyl-CoA:3-ketoacid-CoA transferase (SCOT, gene name *Oxct1*) deficient (*Oxct1*$^{Muscle-/-}$) mice and their control littermates were fed a low-fat diet (lean) or high-fat diet (obese) for 12 weeks. Animals were randomized to receive treatment with either vehicle control or potential SCOT antagonists identified through in silico molecular modeling, while glucose homeostasis (glucose/insulin tolerance testing) and whole-body energy metabolism (indirect calorimetry) were assessed.
Results: We report herein that activity of the rate-limiting-enzyme for ketone body oxidation, SCOT, is increased in skeletal muscle during experimental obesity in mice. In vitro assays and working heart perfusions confirmed that 1 of our hits (pimozide) inhibits SCOT and subsequently reduces ketone body oxidation, respectively. We further determined that increased skeletal muscle SCOT activity/ketone body oxidation contributes to the pathology of T2D, as pimozide treatment improved glucose tolerance in obese mice, which was phenocopied in obese *Oxct1*$^{Muscle-/-}$ mice. Moreover, these improvements in glycemia secondary to reductions in skeletal muscle ketone body oxidation were dependent on obesity, as lean pimozide treated and lean *Oxct1*$^{Muscle-/-}$ mice exhibited similar glucose tolerance profiles as their control treated and control littermates, respectively. Additionally, both pimozide treatment and obese *Oxct1*$^{Muscle-/-}$ mice were associated with increased respiratory exchange ratios during indirect calorimetry studies.
Conclusion: This work defines a fundamental contribution of enhanced muscle ketone body oxidation to the pathology of obesity-induced dysglycemia/T2D, while identifying SCOT inhibition as a novel target for glucose lowering.

Abstract C2

Skeletal Muscle Ketone Body Metabolism Regulates Glycemia During Experimental Obesity

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Purpose: Type 2 Diabetes (T2D) is a rapidly growing health epidemic, with intense investigation on whether perturbations in skeletal muscle carbohydrate and fatty acid metabolism contribute to obesity-induced T2D. Conversely, whether perturbations in skeletal muscle ketone body metabolism also contribute to obesity-induced T2D has been comparatively understudied. However, this is becoming more relevant due to the increased willingness of individuals to consume a ketogenic diet as a non-pharmacological strategy for weight loss and improved glycemic control. We hypothesized that succinyl CoA:3-ketoacid CoA transferase (SCOT), the rate limiting enzyme of ketone body oxidation, would be elevated in skeletal muscles from obese mice and contribute to the pathology of obesity-induced dysglycemia.

Methods: We placed C57BL/6J mice on a low-fat (lean) or high-fat (obese) diet for 12 weeks, following which animals were euthanized and gastrocnemius muscles were extracted for assessment of SCOT mRNA/protein expression via real-time PCR (qPCR)/western blotting methods. Moreover, we also subjected muscle-specific SCOT knockout ($SCOT^{MuscleKO}$) mice and their wild-type (WT) littermates to experimental obesity. Last, we cultured C2C12 myotubes and utilized siRNA or plasmid-mediated transfection approaches to modify SCOT, following which we assessed the expression of key regulators of mitochondrial metabolism via both qPCR and western blotting.

Results: Obese mice demonstrated a marked increase in SCOT mRNA/protein expression within gastrocnemius muscles, which was associated with an increase in SCOT enzymatic activity. Intriguingly, $SCOT^{MuscleKO}$ mice were protected against obesity-induced dysglycemia versus their WT littermates. Furthermore, muscles from $SCOT^{MuscleKO}$ mice and SCOT knockdown in C2C12 myotubes both resulted in increased protein succinylation (regulator of mitochondrial metabolism) and decreased PDH phosphorylation (regulator of glucose metabolism). Conversely, protein succinylation was decreased and PDH phosphorylation was increased in C2C12 myotubes following overexpression of SCOT.

Conclusions: Our results suggest that perturbations in muscle ketone body metabolism contribute to obesity-associated dysglycemia.

Supported by: FoPPS Summer Studentship, AIHS.

Abstract C3

FOXO1 Inhibition Mitigates Diabetic Cardiomyopathy Via Stimulating Myocardial Pyruvate Dehydrogenase Activity and Glucose Oxidation

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Purpose: Cardiovascular diseases including diabetic cardiomyopathy represent a major cause of death in type-2 diabetes (T2D) patients. In T2D, previous studies have shown that myocardial glucose oxidation (GOx) rates are markedly impaired and the activity of forkhead Box O1 (FoxO1) is enhanced, with increased expression of its target-gene pyruvate dehydrogenase (PDH) kinase 4 (*Pdk4*), which phosphorylates and inhibits PDH, the rate-limiting-enzyme of GOx. Our aim was to determine whether FoxO1 antagonism could mitigate diabetic cardiomyopathy through stimulation of PDH activity/GOx.

Methods: To address this, C57BL/6J or cardiac-specific *Pdha1* deficient (*Pdha1*$^{Cardiac-/-}$) and myosin heavy chain α (αMHC)-Cre male mice were subjected to experimental T2D and treated for 2-weeks with either vehicle or AS1842856 (100 mg/kg twice-daily). Energy metabolism and cardiac function were assessed via isolated working heart perfusions and ultrasound echocardiography, respectively.
Results: FoxO1 inhibition in C57BL/6J mice with T2D alleviated diastolic dysfunction as reflected by increases in the mitral E/A and tissue Doppler E'/A' ratios. Conversely, we observed no change in parameters of systolic function (e.g. LVEF). Moreover, FoxO1 inhibition decreased *Pdk4* mRNA/protein expression (~60%), which correlated with a decrease in PDH phosphorylation and increase in PDH activity. Consistently, we observed a marked increase in glucose oxidation and decrease in palmitate oxidation in isolated working hearts from AS1842856 treated mice with T2D. Intriguingly, the improvement in diastolic function in response to FoxO1 inhibition was abolished in *Pdha1*$^{Cardiac-/-}$ mice, but was still observed in αMHC-Cre mice.
Conclusions: Our results suggest that FoxO1 inhibition mitigates diabetic cardiomyopathy via increasing myocardial PDH activity/glucose oxidation.

Abstract C4 (oral presentation, poster not judged)

Cardiac Glucose Oxidation Rates are Impaired and a Possible Pharmacological Target for Mitigating Heart Failure in Barth Syndrome

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Purpose: Heart failure presents as the leading cause of infant mortality in individuals with Barth syndrome (BTHS), a rare genetic disorder fist described by Peter Barth and colleagues in 1983. The causative mutation underlying the BTHS phenotype has been mapped to the tafazzin (*TAZ*) gene, which encodes for a phospholipid transacylase critical in the remodelling of the mitochondrial phospholipid, cardiolipin. Despite well-characterized mitochondrial dysfunction, information regarding alterations of cardiac energetics in BTHS-affected individuals remains limited. Hence, our objective was to identify potential metabolic perturbations and determine whether optimization of cardiac energy metabolism may be a novel approach to attenuate cardiomyopathy development in BTHS.
Methods: Cardiac function in a mouse model of BTHS (tetracycline-inducible *Taz* knockdown (TAZKD) mice) was assessed through ultrasound echocardiography in mice ~2 months of age. Hearts were extracted from ~2.5-month-old TAZKD mice and their wild-type littermates for mRNA/protein expression profiling, or for isolated working heart perfusions to assess energy metabolism.
Results: TAZKD mice exhibited hypertrophic cardiomyopathy as evidenced by increased left ventricular (LV) anterior (0.95±0.04 vs. 0.82±0.03 (mm)) and posterior (0.85±0.05 vs. 0.79±0.09 (mm)) diastolic wall thickness, and impaired LV systolic/diastolic volumes. Conversely, systolic dysfunction was not apparent. Of interest, inhibitory phosphorylation of pyruvate dehydrogenase (PDH), the rate-limiting enzyme for glucose oxidation, was increased in TAZKD mice hearts. This change coincided with increased protein expression of PDH kinase 4 (PDHK4), the primary PDHK isoform in the heart inhibiting PDH activity. Moreover, TAZKD mouse hearts exhibited a reduction in glucose oxidation rates. Treatment with the pan-PDHK inhibitor, dichloroacetate, decreased inhibitory phosphorylation of PDH in TAZKD mice, though its impact on cardiac function remains to be assessed.
Conclusions: Our findings point to a reduction in myocardial glucose oxidation prior to the development of HF in TAZKD mice, which may represent a pharmacological target for mitigating HF development/progression in BTHS.

Abstract C5

Pyruvate dehydrogenase affects regulation of oxidative stress

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Purpose: Previous work from our laboratory has demonstrated that mice with a skeletal muscle-specific deficiency of pyruvate dehydrogenase (PDH), the rate-limiting-enzyme of glucose oxidation, have increased mortality, elevated lactic acid, and reduced exercise tolerance with depleted reduced glutathione levels. As reduced glutathione plays a key role in regulating oxidative stress, the present study sought to determine how PDH affects the expression of pro- and anti-oxidant genes.
Methods: C57BL/6 mice with and without inducible, skeletal muscle-specific knock-out of PDH ($PDH^{Muscle-/-}$ mice) were fed either a low-fat diet (LFD) or high-fat diet (HFD). HFD fed $PDH^{Muscle-/-}$ mice and their control littermates (human skeletal actin (HSA)-Cre) were either subjected to forced exercise (exercise, n=4 from each genotype) or a lack of exercise (sedentary, n=4 from each genotype). LFD mice were allowed to either feed (fed, n=4 from each genotype) or fast (fasted, n=4 from each genotype). Following the exercise or diet manipulation, all mice were euthanized and soleus muscles were extracted and snap frozen in liquid nitrogen. RNA was extracted from the frozen muscle samples and analyzed for the expression of anti-oxidant and pro-oxidant genes using real-time PCR.
Results: All observed anti-oxidant and pro-oxidant genes were reduced in exercised HSA-Cre mice when compared to their sedentary counterparts. However, exercise increased the gene expression of pro-oxidant NADPH oxidase 2 in $PDH^{Muscle-/-}$ mice. Compared to fasted HSA-Cre mice, fasted $PDH^{SkM-/-}$ mice had elevated gene expression for catalase and peroxiredoxin 1 and 6.
Conclusions: The elevated gene expression of NADPH oxidase 2 in exercised $PDH1^{SkM-/-}$ is consistent with their reduced glutathione levels. Taken together, these observations suggest that muscle PDH activity is an important factor in managing oxidative stress.

Abstract C6

Elucidating the mechanism by which the antianginal ranolazine mitigates obesity-induced nonalcoholic fatty liver disease

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Purpose: Nonalcoholic fatty liver disease (NAFLD) is defined as the presence of excess fat (steatosis) in the liver, due to non-alcohol abuse. The prevalence rate of NAFLD is increasing at an alarming rate, and specifically in affects approximately 7 million individuals. In addition, NAFLD is strongly associated with increased risk for type 2 diabetes, insulin resistance, and dyslipidemia, which may contribute to cardiovascular diseases such as, hypertension and coronary artery disease (e.g. angina). Interestingly, ranolazine is a second-line antianginal agent has been shown to improve glycemia, and we have previously demonstrated that ranolazine also reverses the progression of obesity-induced NAFLD. However, the mechanism by which it reverses NAFLD remains elusive. As we have shown that ranolazine increases hepatic pyruvate dehydrogenase (PDH) activity, the rate-limiting-enzyme of glucose oxidation, our goal was to determine whether increases in PDH activity may explain how ranolazine decreases hepatic steatosis.
Methods: In order to address our hypothesis, we will generate mice with a hepatocyte-specific deletion of PDH. We plan to supplement these mice and their control littermates with a low-fat diet or high-fat diet for 10-weeks. All mice will be randomized to treatment with either ranolazine (50 mg/kg) or vehicle control (saline) for 30-days, following which we will assess glucose homeostasis and hepatic steatosis.

Results: We have successfully generated a hepatocyte-specific PDH knockout (KO) mouse model by crossing albumin-Cre mice with our floxed PDH mouse line. These animals demonstrate virtually absent PDH expression in their livers, while maintaining normal PDH expression in other peripheral tissues.
Conclusion: Our results indicate that ranolazine has favourable actions on NAFLD and blood sugar control in obesity. Thus, our future goals are to determine whether hepatic PDH activity explains these salutary actions of ranolazine through use of our new hepatocyte-specific PDH KO mouse model.

Abstract D1 (oral presentation, poster not judged)

Cytochrome P450-Derived Epoxy Lipids of N-3 PUFAs Protect the Heart From Ischemia-Reperfusion Injury by Regulating Mitochondrial Sirtuin 3

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Purpose: Maintaining mitochondrial quality has emerged as a crucial therapeutic strategy to ameliorate myocardial ischemia-reperfusion (IR) injury. The mitochondrial deacetylase sirtuin 3 (SIRT3) plays a pivotal role in the maintenance of mitochondrial function through regulating the mitochondrial acetylome, enhancing the antioxidant defense mechanisms and modulating energy metabolism. Our recent data demonstrate that the cytochrome P450 (CYP) epoxygenase-derived metabolite of docosahexaenoic acid (DHA, n-3 PUFA), 19,20-epoxydocosapentaenoic acid (19,20-EDP), exhibits protective effects toward cardiac mitochondria, however; the mechanism(s) remain unknown. We hypothesize that the cardioprotective mechanism(s) of 19,20-EDP against IR injury involve regulating mitochondrial SIRT3.
Methods: Langendorff and isolated working heart perfusions were performed in male and female C57BL/6 mice to assess changes in cardiac function and energy metabolism in response to IR injury. Mice were perfused with either vehicle, 19,20-EDP (1 µM) and/or the SIRT3 inhibitor nicotinamide (30 µM). SIRT3 activity and total lysine acetylation levels were determined in cardiac tissues. The direct effect of 19,20-EDP on mitochondrial respiration was assessed in human ventricular tissues obtained from individuals with ischemic heart disease (IHD) included in the Human Explanted Heart Program and compared to non-failing control hearts (NFC).
Results: Acute 19,20-EDP administration improved cardiac recovery following IR injury, which was accompanied by enhanced glucose oxidation rates and improved cardiac efficiency. The observed cardioprotective effects were associated with enhanced SIRT3 activity and reduced global protein/lysine acetylation. Notably, we observed increased acetylation and reduced activity of the mitochondrial antioxidant superoxide dismutase (MnSOD) in the ischemic human myocardium. Treatment with 19,20-EDP also improved mitochondrial respiration in permeabilized human fibers obtained from IHD hearts. 19,20-EDP cardioprotective effect was abolished by the SIRT3 inhibitor nicotinamide.
Conclusion: Together, these data demonstrate that 19,20-EDP-mediated cardioprotective mechanisms involve preservation of mitochondrial SIRT3 activity, which results in improved cardiac efficiency.

Abstract D2

Genetic Deletion of Soluble Epoxide Hydrolase Preserves Cardiac Function in Aged Female Mice

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Purpose: Aging is a key determinant of cardiovascular health associated with slowly progressive decline in cardiac function. Yet, our understanding of involved mechanisms and sex differences is limited. There is growing evidence indicating CYP450 epoxygenase-mediated metabolites of n-3 and n-6 polyunsaturated fatty acids mediate cardiac function. These epoxy metabolites are rapidly metabolized by soluble epoxide hydrolase (sEH). The current study aims to characterize cardiac function in young and aged sEH null mice compared to their (WT) counterparts.
Methods: Cardiac function was assessed in both young (2-4 months) and aged (15-18 months) WT and sEH null male and female mice by echocardiography. Western blotting was done to measure changes in protein expression of p-Akt, acetyl Mn-SOD, sEH, and mEH. Protein carbonyl level and SOD activity were determined in the hearts of experimental animals. Electron microscopy was used to assess mitochondrial ultrastructure.
Results: Significant increase in heart weight: tibia length was observed in all aged groups except female sEH null mice. There was a marked decline in cardiac function in aged WT mice both females and males. Interestingly, female aged sEH null mice demonstrated preserved cardiac function. There was an increase in protein expression level of p-Akt in all aged mice. Sirt-3 activity significantly decreased over aging in WT both males and females associated with increased expression level of acetyl Mn-SOD. Genetic deletion of sEH preserved sirt-3 activity coupled with lower level of acetyl Mn-SOD in the hearts of both female and male mice. With aging, the activity level of SOD decreased in male animals both WT and sEH null. There was an age-related disruption in mitochondrial ultrastructure in WT animals which was attenuated is sEH null mice.
Conclusion: Together these data demonstrates the beneficial effects of genetic deletion of sEH in limiting age-related cardiac alterations are more robust in female mice.

Abstract D3

Cardiac-specific genetic deletion of soluble epoxide hydrolase preserves cardiac function in a murine model of acute lipopolysaccharide-induced sepsis

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Purpose: Acute systemic inflammatory syndromes, such as sepsis, elicit a detrimental multi-organ inflammatory response. The heart is particularly susceptible to the effects of acute inflammation, with myocardial dysfunction accounting for a significant proportion of deaths due to severe sepsis. Epoxyoctadecenoic acids (EpOMEs), endogenously derived lipid mediators from linoleic acid, are metabolized by the cytosolic enzyme, soluble epoxide hydrolase (sEH), to dihydroxyoctadecenoic acids (DiHOMEs). Research shows that DiHOME accumulation causes mitochondrial damage and loss of cardioprotection. Inhibition of sEH evokes anti-inflammatory responses and activates prosurvival cell signaling pathways. This preliminary study investigated whether whole-body and cardiac-specific genetic deletion of sEH can preserve cardiac function in an acute inflammatory model of sepsis.
Methods: Young (2-5 months) male WT and whole-body sEH knockout (KO) mice were utilized. Cardiac-specific sEH KO were produced using a tamoxifen-inducible Cre lox system. Mice were injected intraperitoneally with lipopolysaccharide (LPS) toxin (10mg/kg) or normal saline. Baseline echocardiography was performed 4 days before treatment and 23 hours post-LPS injection. Frailty indices, body temperature, and body weight measurements were conducted pre-injection and 23 hours post-LPS. Mice were sacrificed and tissues harvest 24 hours post-LPS administration.

Results: Cardiac functional parameters, including left ventricular systolic function and ejection fraction, were preserved in cardiac-specific and whole-body sEH KO mice compared to their WT counterparts. Frailty index scores demonstrated reduced signs of frailty and functional impairment in both sEH KO models compared to WT post-LPS administration.
Conclusions: Cardiac-specific and full-body genetic deletion of sEH preserves cardiac function in a model of acute inflammatory sepsis. Inhibition of sEH serves as a potential pharmacological target to modulate the lipid metabolite profile to preserve cardiac function. The ability to specifically knockout sEH in cardiomyocytes may allow for targeted cardiac-specific protection without extra-cardiac manifestations of a whole-body knockout. Support: This research is supported by NSERC

Abstract E1 (oral presentation, poster not judged)
Cross-Validation of SHP2 Inhibitors Identified through Computational Methods
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Purpose: The Src homology region 2 (SH2)-containing protein tyrosine phosphatase 2 (SHP2) protein plays an important role in signal transduction from the cell surface to the nucleus. SHP2 is a cancer driver, and its overstimulation is a key player in juvenile myelomonocytic leukemia and triple negative breast cancer. Here we focus on identifying novel drug-like molecules that inhibit the activity of SHP2 and represent validated starting points for the design of novel therapeutic agents for these conditions.
Methods: Structure-based computational database screening has been used to filter libraries of millions of small molecules for their ability to interact with the allosteric regulatory sites or the lipid-binding sites of SHP2. Thirty-eight short-listed ligands were tested for activity using recombinant SHP2 protein containing the two SH2 domains and the catalytic domain. The experiments used for cross validation included protein thermal shift (PTS), phosphatase activity, size exclusion chromatography multi-angle light scattering (SEC-MALS), and surface plasmon resonance (SPR) detection.
Results: Eight compounds were found to consistently decreased SHP2's activity and demonstrated binding in at least two assays. Further experiments identified two compounds that are tight binders and inhibitors of SHP2. One compound exhibited an average KD of 115 nM by SPR, which is 20-fold stronger than a known SHP2 inhibitor, NSC-87877, which exhibits a KD of 2324 nM.
Conclusions: This project demonstrates the importance of integrating structure-based drug design screening by computational methods and cross-validation with biophysical techniques. Efficient identification of potential inhibitors opens doors to future chemical modifications in order to improve affinity, selectivity and inhibitory action, and could lead to novel therapeutic agents in the future.
Support: Alberta Cancer Foundation Summer Studentship.

Abstract E2
Modelling the PAS B domain of the Aryl Hydrocarbon Receptor
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Purpose: The aryl hydrocarbon receptor (AhR) is a ligand-activated transcriptional factor, and regulates the expression of various genes. It is well established to play a promoting role in the initiation, promotion, progression, invasion, and metastasis of cancer cells. The full-length AhR encompasses various domains, including bHLH, PAS A, PAS B & transactivation domain. The PAS B domain plays a key role in regulating the activity of AhR by interacting with either AhR agonists/antagonists through its ligand-binding domain (LBD). Here we focus on using computational modelling to study the structure of the PAS B region and understand its LBD.

Methods: As the crystal structure of the PAS B domain is not available, we used different homology modelling algorithms to build a 3-dimensional (3-D) structure for this region. Our building process involved several steps, including: template identification, target-template alignment, model building, and model validation.
Results: The crystal structures of human hypoxia inducible factor (HIF-2α) (PDB code: 5TBM), and (HIF-1α) (PDB code: 4H6J) were used as templates to build different models for the PAS B domain, and have a sequence similarity to PSA B of ~ 27% and 31%, respectively. Seventeen different PSA B models were built. Fifteen models were constructed based on the two templates using Swiss model, MOE, i-TASSER, and phyer2 software packages. The other two models were generated using an ab initio modeling algorithm as implemented in i-TASSER and phyer2. The models were validated using several tools, and two models showed acceptable scores.
Conclusions: The PSA B domain of the AhR contains LBD. Two models showed acceptable 3-D parameters and will be used to understand how the PSA B domain regulates the function of AhR. This will lead to the development of new therapies for the treatment cancer.

Abstract E3

Prostaglandin E2 promotes angiogenesis in ovarian endometriosis by regulating Matrix Metalloproteinase-2

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Background: Endometriosis is a painful gynecological disorder that affects 10-15% of reproductive women. It is an ectopic development of functional endometrial glands and associated with dysregulated matrix metalloproteinases activity, inflammation and pathological angiogenesis. However, how MMP-2 is involved in the development of ovarian endometriosis is not clearly known.
Materials and Methods: Our study was comprised of 93 ovarian endometriosis samples of different stages and evaluated MMP-2 activity in serum and ectopic tissues. Zymography was performed for MMP-2 activity analysis. Western blots were performed for expression of different angiogenic factors. All in vitro studies were performed using HUVEC cell line.
Results: Severity-dependent upregulation of MMP-2 activities was observed only in the ectopic tissues. These endometriosis glands were positive for estrogen receptor and showed severity dependent upregulation of cycloxygenase (COX)-2 expression. The ectopic expressions for VEGF and VEGFR-2 were increased, along with Von Willebrand Factor. As activation of MMP-2 (from pro to active form) depends on MT1MMP and TIMP-2, we further looked into these molecules. The expression for MT1MMP was upregulated, while TIMP-2 was downregulated with the severity of the disease. In ovo-assay (chorioallantoic membrane assay) further confirmed the pro-angiogenic properties for endometriosis, which was inhibited with chemical inhibitors for MMP-2. In addition, in vitro inhibition of MMP-2 attenuated the cellular migration as well as invasion and angiogenic tube formation. Our data was further validated through an in vivo endometriosis mouse model to found that the activation of MMP-2 involved limited MMP-2-TIMP-2 interaction.
Conclusion: Our study confirms the essential involvement of active MMP-2 in pathological angiogenesis during ovarian endometriosis.
Support: CSIR, INDIA.

Abstract E4

Identifying the mechanism of action for a potent small molecule immunomodulator

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Purpose: Cancer immunotherapy has emerged as the fourth pillar of cancer treatment along with surgery, radiation, and chemotherapy. Immunotherapeutic approaches utilize components of a patient's own immune system to selectively target cancer cells. Stimulating the immune system to fight the tumor plays an important role in nearly all aspects of cancer immunotherapy. The objective of our study is based on developing accessible and potent cancer immunotherapy small-molecule drug.
Methods: In our study, a heterocyclic compound (Compound-A) was studied for its immunostimulatory effects using peripheral blood mononuclear cells (PBMCs) collected from healthy volunteers. The effects of the compound-A on proliferative capacity and interleukin-2 (IL-2) secretion ability of T cells were determined by carboxyfluorescein succinimidyl ester (CFSE) staining and ELISA, respectively. In addition, microsomal stability of the compound in human liver microsomes and its potential toxicity against PBMCs was determined using CellTiter-Glo®-Luminescent Assay, Finally, the impact of compound A on the regulation of different gens was studied using RNA sequencing approach.
Results: Compound-A enhanced immune responses by increased T cells proliferation and IL-2 secretion. Compound-A metabolic stability showed that 59.6 % was remaining after 60 min. No cytotoxicity was shown against PBMCs. A total of 792 differentially expressed genes (DEGs) were identified after treating PBMCs with the compound-A for 12 hours, including 377 upregulated and 415 downregulated genes. Also, a total of 863 DEGs were identified after 24 hours treatment, including 444 upregulated and 419 downregulated genes. GO and genome pathway analysis showed that these DEGs were enriched in signaling pathways associated with response to interferon-gamma.
Conclusions: Our study confirmed the immunostimulatory activities of the Compound-A. Further analyses are required to confirm the molecular pathways underlying activity of this compound as an effective anticancer treatment. A future direction will be to identify and validate the molecular targets responsible for its immunological activities.

Abstract E5

Effect of Platelets on Cancer Cell Immune Checkpoint PD-L1 Expression

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Purpose: Platelets have the potential to induce Programmed Death Ligand 1 (PD-L1) expression on cancer cells, and this may allow cancer cells to evade destruction by the immune system by causing T-cell anergy and/or apoptosis. However, the mechanism(s) through which this may occur is unknown. This project investigated the platelet-secreted factors or direct platelet binding to lung cancer cells upregulates lung cancer cell PD-L1. We hypothesized that platelet-secreted vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) increase cancer cell PD-L1 expression as VEGF and PDGF stimulate STAT-signalling, which is known to regulate PD-L1 expression.
Methods: Platelets were isolated from healthy human volunteers and cultured with human A549 lung cancer cells and the protein translation inhibitor cycloheximide for 24 hours. A549 cells were also cultured with diluted platelet releasates and small molecule inhibitors of vascular endothelial growth factor receptor (VEGFRi 10uM) (SU5416) and platelet-derived growth factor receptor (PDGFRi 5uM) (AG1296) for 24 hours. A549 and platelet surface PD-L1 expression was measured using flow cytometry.
Results: Platelets stimulated A549 PD-L1 expression that was not inhibited by cycloheximide (2.3±0.6% vs. 7.2±1.3% vs. 8.8±1.3% PD-L1 positive A549, $P < 0.01$). Additionally, cycloheximide was noted to cause apoptosis-like changes in A549. Following incubation with platelets, two-colour flow cytometry measuring the platelet marker CD-41b and PD-L1 demonstrated that only 1.2±0.6% of A549 were CD41b

and PD-L1 positive. Similarly, only 2.0±0.2% of platelets were PD-L1 positive. When incubated with platelet releasates, PD-L1 was detected on 10.13±1.5% (control), 9.16±0.81% (releasate only), 7.39±1.0% (releasate and VEGFRi), 7.89±1.2% (releasate and PDGFRi) (P=0.08) of A549.
Preliminary conclusions: Platelet released factors may predominantly contribute to the increased expression of PD-L1 on cancer cells. Apoptosis itself may increase cancer cell PD-L1 expression.

Abstract F1 (oral presentation, poster not judged)
Medication deprescribing for seniors: Economic advantage or financial barrier?
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PURPOSE: Polypharmacy is a major trigger for potentially inappropriate medications (PIM), which may lead to poor outcomes for seniors. One solution is to use deprescribing. However, several barriers may oppose this process, including pharmacy financial disincentives. The purpose of this study is to determine the cost of deprescribing on the pharmacy, public payer (government), and the patient, across Canadian provinces and territories.
METHODS: A standard case was developed to reflect an 'average' senior in Canada, at median income, with common multimorbidities, medications frequently used in seniors, and one high-cost medication. 8 different deprescribing scenarios were studied financially, while abstracting detailed drug costs from the different government plans covered in each jurisdiction, and calculating the annual average pharmacy margin difference and total government and patient share. Costs were calculated for a 1-year period.
RESUL TS: The baseline patient cost for the regimen ranged between $378 - $1093/year. The scenario with the greatest cost saving to the patient and greatest loss to the pharmacy was switching to a lower cost medication from Liraglutide to prefilled Detemir, with highest savings in patient share of $3479 in Ontario and highest loss difference in pharmacy margin of $393 in Newfoundland and Labrador**.**
CONCLUSION: There is a range in costs and coverage for medications across Canada. The deprescribing scenarios demonstrated a small impact on the pharmacy's gross margin, in some cases a significant financial impact on patient costs, but minimal impact to government. Deprescribing initiatives and policies should include financial considerations for community pharmacies and patients.

Abstract F2
International comparison of community pharmacists' sexual and reproductive health roles and attitudes
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Purpose: To explore and compare pharmacists' roles and attitudes towards provision of sexual and reproductive health (SRH) services, self-reported confidence and training preferences in three countries (Japan, Thailand, Canada).
Methods: An email to complete a web-based questionnaire will be sent to community pharmacists. Contact information will be obtained from The Alberta College of Pharmacy and Japanese and Thai community pharmacists associations. The instrument will include face and content validity stages, as well as test-retest reliability and pilot testing in a small sample of the representative population. The survey will be translated from English to Japanese and Thai languages, and it will be available for a duration of 4 weeks with two reminder emails. An incentive to complete the survey will be provided.

Results: A literature review was conducted to inform survey development. The review considered studies that explored, described, and evaluated pharmacists' attitudes, practices, and roles in providing SRH services. To date, the survey instrument has been developed and reviewed by experts in each country for content validity and consideration of pharmacists' scope of practice. The survey consists of six sections: (1) provision of SRH services, (2) attitudes toward SRH services, (3) factors that influence SRH services, (4) self-reported confidence in providing education related to SRH, (5) SRH competencies and training preferences, and (6) demographics. The instrument covers 9 areas: pregnancy tests, ovulation tests contraception (non-hormonal and hormonal), emergency contraception, sexually transmitted infections, maternal and perinatal health, and general sexual health. Questions related to HIV pre-exposure prophylaxis (PrEP), administration of injections, and prescribing are included for Alberta to reflect the scope of practice.
Conclusions: Pharmacists are well-positioned to provide SRH services as knowledgeable and accessible healthcare providers. This survey will help to understand attitudes of pharmacists towards SRH, current practices, and learning preferences and inform future research and educational programs.

Abstract F3 (oral presentation, poster not judged)
Exploring cannabis use for medical purposes and related risks in women's health: A scoping review
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Purpose: With the recent Canadian legalization, cannabis has become more socially accepted with increased patient interest in its use for medical purposes. Clinical guidelines on medical cannabis currently do not address its role in managing women's health conditions. Our objectives were to explore existing scientific literature to summarize published evidence on cannabis use for medical purposes in women's health, identify findings in this population on related risks, and describe portrayed women's perspectives.
Methods: We completed a scoping review using the PRISMA-ScR guideline. Electronic databases were systematically searched (inception to September 2018) for relevant articles in primary and grey literature. Keywords were derived from cannabis and women's health topics, including "cannabis, marijuana, cannabinoids" and "menstruation, perinatal, maternal, menopause". Recreational and medical cannabis was included within the search. Titles/abstracts were initially screened by two independent reviewers, followed by full-text review. Articles excluded were: non-English, review articles or conference abstracts, pediatric populations, and studies specific to cannabis use disorder, withdrawal effects or policy development. Data was extracted to provide narrative summaries and categorization of evidence to date.
Results: Our search yielded 3033 results, of which 43 articles met the inclusion criteria. Articles were categorized by reproductive health stage of the studied population: menstruation (n=6), pregnancy (n=24), breastfeeding (n=2), menopause (n=3), and the remaining investigated sex differences between males and females (n=7) or did not specify the reproductive health stage. Studies were from the United States (n=34) or Canada (n=6) and other (n=3). Currently in progress are narrative summaries to outline the medical purposes and risks studied in the captured literature.
Conclusions: There is a lack of evidence on cannabis for therapeutic use in women's health. Future work in understanding the experiences of women who use cannabis for women's health-related conditions will provide insight into cannabis use for medical purposes.

Abstract F4
Beers and Genes: a Look at Pharmacogenomics and Beers® Criteria Medications
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Purpose: Pharmacogenomics (PGx) has been discussed in younger patients with niche medical conditions, with little research in older adults. Although there are tools that identify mediations that may be unsafe in older adults, namely with the Beers® Criteria, it has not been evaluated in terms of PGx implications. The first objective of this study was to determine the prevalence of PGx-testable medications used by older adults with a stable medication regimen, in an inpatient, rehabilitation setting. The second objective was to determine the proportion of the Beers Criteria® 2019 medications that have available pharmacogenomic testing.
Methods: International reference standards were used to identify medications that had PGx information, then cross-referenced with the Beers® Criteria 2019. Inpatient data from a rehabilitation hospital was obtained in July 2019, for adults age 65 years and over; this was reviewed and medications that were on the Beers Criteria, or could undergo PGx testing, were identified.
Results: A table of 42 PGx-testable medications were identified, with 37 (88%) of those appearing on the Beers® Criteria. There was 142 patients eligible, 114 (80%) using at least 1 Beers Criteria® medication; 88 (62%) were using a medication with PGx testing available, and 65 (46%) using medications that were including on both Beers Criteria® and PGx lists.
Conclusions: Current older adult patients admitted in a rehabilitation center were using medications that are eligible for PGx testing. Most of the PGx-testable medications are on the Beers Criteria, which may explain some of the safety concerns in older adults. Further clinical research is required to determine the implications PGx testing in older adults, and the relationship with medication safety.

Abstract F5

COPD case-finding services by healthcare practitioners: a scoping review.

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Purpose: Early detection of Chronic Obstructive Pulmonary Disease (COPD) is one of the strategies to address increasing burden of this costly chronic condition. We aim to provide an overview of the published literature on COPD case-finding services by healthcare professionals and to determine strategies in identifying patients at risk, as well as diagnostic yield.
Methods: An extensive literature search was done through Embase, Medline, Cumulative Index to Nursing and Allied Health Literature (CINAHL) and Web of Science from inception to January 2019. Two reviewers independently screened titles and abstracts followed by a full review of potential studies. Studies that met the inclusion criteria were related to new COPD cases, published in English language, and with no restrictions on study designs. Extracted data were organized under the following themes: population characteristics, inclusion and exclusion criteria, setting, case-finding strategies and yield, healthcare practitioners involved, and study recruitment strategies used.
Results: 6,032 unique articles which were identified in the search were screened during the first title/abstract stage. We reviewed 431 full articles and 132 were included for the qualitative synthesis. While analysis is ongoing, diagnostic yield from the case-finding services ranges from 0.5% to 52.1%. We divided the yield into quartiles, which generated 24.2% of the included articles with very low yield (0-6.79%), 25% with a low yield (6.8-12.99%), another 24.2% with a high yield (13-20.674%) and lastly, 26.5% with a very high yield (20.675-52.1%). Variation in yield is dependent on factors such as study population and strategy for case finding.
Conclusion: Various strategies have been deployed by healthcare practitioners in identifying early cases of COPD. Analysis of the strategies can be considered for deployment by community pharmacists due to

their accessibility and expanding scope of practice. This in turn can improve care for patients who may have otherwise remained undiagnosed.

Abstract F6
Systematic Review of Brivaracetam in Patients with Status Epilepticus
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Purpose: Brivaracetam (BRV) is an antiepileptic that has been approved for monotherapy or as an adjunctive agent for focal seizures management.[1] It has a unique 2-2-oxo-4-propyl-pyrrolidin-1-yl butanamide structure making it more lipophilic than its chemistry analog levetiracetam.[2] Considering its pharmacokinetic properties, BRV is a plausible option in the setting of status epilepticus, a life-threatening medical emergency. Recent evidence has shown that BRV may demonstrate therapeutic efficacy in status epilepticus (SE).[2-7] The objective of this systematic review was to summarize the available evidence pertaining to the efficacy of BRV use in SE.
Methods: An electronic literature search of Medline, Embase and Scopus databases was performed in May 2019 to identify reports of BRV use in Status Epilepticus. References of selected articles were also examined to identify more articles to be included.
Results: There was a total of 413 records identified through database search and from other sources. Following duplicate removal and abstract and title screening, 41 papers were included for full text assessment for eligibility. After full text assessment, there was a total of 3 retrospective studies and 3 case series that specifically looked at the efficacy of BRV in status epilepticus. Overall, there was a total of 41 patients with SE within the included studies. Brivaracetam was introduced as early as 0.5 hours and as late as 105 days from SE onset. BRV dose ranged from 100-300 mg/day. The total remission rate contributed by BRV was observed in 17 patients (41.4%) who were of relatively younger median age.
Conclusion: Studies showed BRV may be relatively safe with no major adverse events reported that could be more beneficial in younger patients with a higher loading dose starting at 2mg/kg.[2-3,5] The efficacy of BRV in SE might vary depending on etiology, population characteristics and scaling disease severity. Further studies are needed to delineate these variations.

Abstract G1 (oral presentation, poster not judged)
The Impact of Nimodipine Administration through Enteral Feeding Tube on the Outcomes in Patients with Aneurysmal Subarachnoid Hemorrhage
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Purpose: To investigate the effect of different nimodipine administration techniques (feeding tube vs oral) in the first 7 days on incidence of angiographic vasospasm, delayed cerebral ischemia (DCI) and death, as well as, determine the impact of nimodipine administration techniques on patient outcomes over 21 days, and to demonstrate predictors of response to the hemodynamic effect of nimodipine (BP reduction).
Methods: A retrospective chart review of patients with SAH and admitted to University of Alberta Hospital, Edmonton, Canada from January 2016 to December 2018 was carried out.
Results: Eighty-five patients were included in analysis of the study. We found that FT administration was associated with incidence of angiographic vasospasm (OR 8.9, 95% CI 1.0-73.1, p-value 0.042 ROC AUC 0.87, HL-test not significant) in the first week. There was no significant difference between the two administration techniques in on DCI and death in the first week however, there was an association of taking nimodipine by feeding tube with DCI in the period of 21 days (OR 38.1 95% CI 1.4-1067.9 p-value 0.032 ROC AUC 0.92 HL-test not significant).

Conclusions: Further research is needed to investigate the bioavailability of this mode of administration to make sure that the high-grade patients with SAH are getting the benefit of the drug.
Support: There is no funding associated with this work.

Abstract G2 (oral presentation, poster not judged)
High-Quality Data Analysis and Theory in Community Pharmacy Qualitative Research
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Purpose: To evaluate data analysis, theoretical usage, and contribution to theory for published qualitative studies in community pharmacy. An understanding of the intersection between data analysis and theory is a cornerstone for understanding complex findings. Theoretical usage varies from being absent to being integrated throughout the research process. Contributions to theory may include linking the findings and showing their interactions to develop new or modify existing models and theories.
Methods: A systematic literature search was conducted using Ovid MEDLINE to identify original peer-reviewed articles in community pharmacy practice employing qualitative research in 2017. Two authors independently extracted and evaluated the research articles describing their data analysis (i.e., descriptive vs interpretive), use of theory and contribution to theory.
Results: Eighty-three articles were retrieved through the database search (n=83) and after the abstract and full-text screening, 31 articles met study criteria and were selected. Data analysis was descriptive in 27(87%) of the studies and interpretive or partially interpretive in 4 (13%) of the studies. Theory was absent in 19 (60%) and implied, partially integrated or retrospectively applied in 12 (40%) of the studies. Contribution to theory development or modification was absent in 29 (94%) of the studies. Two studies (6.5%) were descriptive yet considered theory to make sense of their findings and contributed to theory.
Conclusion: As data analysis move beyond description to interpretation, conceptual development, and theoretical explanation, there is a higher chance of contributing to theory. Pharmacy practitioners may extend understandings of individual practices to enrich the field and enhance patient care. The use of and/or contribution to theory leads to higher quality research which is essential for practitioners and policymakers to deliver better care that leads to favorable health outcomes.

Abstract G3 (oral presentation, poster not judged)
Poor Medication Adherence Can Appear in the Year Prior to an Incident Depressive Episode
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Purpose: Although depression is an accepted risk factor for poor adherence in diabetes, studies examining this association are either cross sectional or only measure adherence after depression diagnosis. Symptoms of depression likely begin well before diagnosis, which could affect adherence earlier than currently reported. Our objective was to measure medication adherence among newly treated people with type 2 diabetes in the year prior to an incident depressive episode.
Methods: This retrospective cohort study was conducted on new metformin users identified in Alberta Health's administrative data between 2008 and 2018. Our exposure of interest was an incident depressive episode occurring at least one year after metformin initiation. Control subjects were randomly assigned a pseudo depression date from exposed subjects so adherence would be measured at similar time points of diabetes duration. Poor adherence was defined as ≤80% of days covered by metformin within the year prior to the index date. Multivariate logistic regression was used to examine the association between depression and adherence.
Results: Of 165,056 new metformin users identified, 5136 (3%) had an incident depressive episode ≥1

year after initiating metformin. A pseudo depression date could be assigned to 113,560 (68%) control subjects. The mean proportion of days covered was significantly lower for subjects with a depressive episode (55.5% [SD 39.0%]) compared to controls (60.0% [SD 38.1%]) ($p<0.001$). After adjusting for other factors, subjects with a depressive episode were more likely to have poor adherence in the year before the incident depressive episode compared to controls (adjusted odds ratio 1.33; 95%CI 1.25,1.41). **Conclusions**: These results suggest that poor adherence to oral antihyperglycemic medications appears in the year prior to depressive episode. Further research is needed to better help clinicians identify patients with diabetes who may be experiencing early symptoms of depression.

Abstract G4

Patterns of Antihyperglycemic Medication Additions to Metformin in People with Type 2 Diabetes

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Purpose: The introduction of new antihyperglycemic drug classes and emerging evidence from Cardiovascular Outcome Trials (CVOTs) give clinicians different options for intensifying the treatment of type 2 diabetes. This study will elucidate whether the temporal patterns in prescribing second line antihyperglycemic agents to intensify metformin-based therapy reflect the introduction of these new drug classes and the emerging evidence from CANVAS, EMPA-REG OUTCOME, LEADER and other CVOTs.
Methods: Data from Alberta Health administrative databases were used to identify new metformin users between April 2009 and March 2018. Antihyperglycemic medications added to metformin therapy at the first point of treatment intensification were identified and grouped by class. This information was used to determine the proportion of different classes added to metformin in each quarter. We then examined the temporal patterns while considering important milestones: formulary listing date for a new drug class and release date of CVOT results.
Results: Of the 165,056 new metformin users, 69,074 (42%) added an antihyperglycemic medication. Sulfonylureas remained the most common drug class added to metformin throughout this observation period. After their introduction, the three new drug classes demonstrated a persistent increase in the proportion of people adding them to metformin. Notably, there was a dramatic uptake of sodium glucose transporter 2 inhibitor use that preceded publication of the EMPA-REG Outcome Trial.
Conclusion: Despite the emerging evidence of cardiovascular benefit demonstrated in the CVOT trials, the sulfonylurea drug class remains the most common choice for treatment intensification in new metformin users. The next step in this line of research is to compare characteristics of people starting different drug classes and at different time points.

Abstract G5 (oral presentation, poster not judged)

Pharmacy and medical students competence and confidence with prescribing: a cross-sectional study

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Purpose: Previous research has shown that prescribing competence is weakly correlated with prescribing confidence, and has questioned whether undergraduate programs adequately prepare students and junior practitioners for safe and rational prescribing. The goal of this project is to investigate whether there are differences in prescribing competence and confidence between fourth year pharmacy and medical students at the University of Alberta.
Methods: A cross-sectional design was used to measure prescribing competence using five case scenarios and confidence with a survey. All fourth year pharmacy and medical students at the University of Alberta

were eligible to participate. Answers to the cases were graded based on therapeutic appropriateness and inclusion of all legal requirements. The confidence survey assessed self-rated confidence of both assessment and prescribing skills. Chi-square tests were used to compare frequencies of prescribing errors and self-rated confidence responses. The Spearman correlation coefficient (r) was used to explore the correlation between prescribing competence and confidence for both cohorts independently.
Results: Thirty-one pharmacy students and 16 medical students (response rate 24% and 10%, respectively) completed the assessment between December 2018 and March 2019. Pharmacy students had significantly more appropriate prescriptions and fewer inappropriate prescriptions than medical students. Both rated themselves as predominantly confident or very confident with prescribing, however both groups struggled to include all the legal requirements of a prescription. There were no significant correlations between competence and confidence scores.
Conclusion: There are multifactorial differences between pharmacy and medicine students requiring further exploration to improve prescribing competence.

Abstract H1

Modulation of the pro-carcinogen activating enzyme Cyp1a1 by mercury and its organic metabolite methylmercury in C57Bl/6 mice.

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Purpose: Cytochrome P450 1A1 (Cyp1a1) is a hepatic and extrahepatic enzyme that is regulated by the aryl hydrocarbon receptor signaling pathway. With the growing human exposure to heavy metals, emerging evidence suggests that heavy metals exposure alter Cyp1a1 enzyme activity. The importance of Cyp1a1 emerges from the fact that it has been always associated with the metabolism of pro-carcinogenic compounds to highly carcinogenic metabolites. Recently we demonstrated the ability of mercuric chloride (Hg^{++}) in human hepatoma HepG2 cells to significantly decrease the TCDD-mediated induction of Cyp1a1. In this study we investigated the effect of methylmercury (MeHg), the major metabolite of Hg^{++}, on Cyp1a1 in vivo.
Methods: Male C57BL/6 mice were injected interperitoneally with Hg^{++} and MeHg (2.5 mg/kg) in the presence and absence of TCDD (15 μg/kg) at 6hr (for mRNA) and 24hr (for protein level). Real-time PCR and Western blot analysis were used to determine mRNA and protein expression, respectively.
Results: Our results show that Hg^{++} and MeHg alone did not alter the hepatic Cyp1a1 mRNA. On the other hand, TCDD significantly increased Cyp1a1 mRNA by 1850 folds. Interestingly, Hg^{++} and MeHg significantly decreased the TCDD-mediated induction of Cyp1a1 by 95% and 71% respectively.
Conclusions: We demonstrate for the first time that the organic form of mercury, MeHg is capable of modulating the expression of TCDD-mediated Cyp1a1 induction. Support: This work was supported by the Natural Sciences and Engineering Re-search Council of Canada (NSERC) Discovery Grant RGPIN 250139–07 to A.O.S.E. MA is the recipient of Saudi Government Scholarship.

Abstract H2

Cannflavin A is a Potential Substrate of the Neutrophil Pro-inflammatory Enzyme, Myeloperoxidase

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Purpose: Cannabinoids are a group of molecules that act on cannabinoid receptors, and are found in commercial hemp products. Cannflavins A and B are a class of prenylated flavonoid compounds that are

unique to *Cannabis sativa* which are reported to have anti-inflammatory benefits gaining recent interest. The aim of this study is to investigate the effect of cannflavin A on myeloperoxidase (MPO), a key anti-inflammatory enzyme.

Methods: A cannflavin A preparation was characterized using high performance liquid chromatography (HPLC) analysis to determine purity. The effect of cannflavin A on the MPO peroxidation cycle was examined by kinetic measurements of spectral changes in the heme active site (430 – 460 nm) using UV-visible spectroscopy to investigate whether cannflavin A is a substrate of MPO. MPO-mediated metabolism of cannflavin A in the absence and presence of reduced glutathione was studied using UV-visible spectroscopy and electron paramagnetic resonance (EPR) spectroscopy with 5,5-Dimethyl-1-pyrroline-N-oxide (DMPO) as a spin-trapping agent.

Results: HPLC/MS analysis of the preparation showed an m/z peak conforming to cannflavin A, and HPLC/UV confirmed its purity to be 95.5%. Addition of cannflavin A to the reaction of MPO and hydrogen peroxide (H_2O_2) significantly enhanced the reduction of MPO compound II back to resting MPO. An MPO-catalyzed cannflavin A free radical was detected by spin trapping using EPR spectroscopy; these species appeared to oxidize glutathione into glutathionyl radical. Moreover, a characteristic peak of a possible dimerized product of cannflavin A was also observed.

Conclusions: This study, for the first time, reports that cannflavin A is an efficient substrate for MPO and MPO/H_2O_2 metabolized it into cannflavin A radical. The implications of cannflavin A metabolism on the cellular inflammatory responses will be further investigated.

Abstract H3

Modulation of cytochrome P450 1A1 (CYP1A1) expression by monomethylmonothioarsonic acid ($MMMTA^V$) in human HepG2 cells

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Purpose: Arsenic is ubiquitous in the environment and millions of people around the globe are exposed to it through contaminated water, rice, or seafood. Arsenic is tightly associated with various health problems including cancer. Thioarsenicals have been detected in the urine of arsenic-exposed humans and animals suggesting their involvement in arsenic toxicity. Both inorganic arsenic and its methylated metabolites have been shown to modulate aryl hydrocarbon receptor (AhR)-regulated cytochrome P450 1 family; a well-known group of enzymes which are strongly involved in the mechanistic pathways of cell toxicity and carcinogenicity. However, little is known about thiolated arsenic metabolites. In this study we examined the impact of monomethylmonothioarsonic acid ($MMMTA^V$) on CYP1A1 which is the archetypal biomarker of AhR activation.

Methods: Human hepatoma (HepG2) cells were treated with $MMMTA^V$ (1, 5 and 10 μM) in the absence and presence of 1 nM 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). CYP1A1 expression was determined at both mRNA and protein levels using qPCR and Western blot analysis, respectively. MTT Assay was used to assess cell viability.

Results: Our results show that cell viability wasn't affected by all concentrations of $MMMTA^V$ used. $MMMTA^V$ alone didn't significantly alter CYP1A1 at mRNA and protein levels, whereas TCDD alone significantly increased CYP1A1 mRNA and protein levels by 150 folds and 1160 folds, respectively. On the other hand, $MMMTA^V$ caused a concentration-dependent decrease of TCDD-mediated induction of CYP1A1 at mRNA and protein levels.

Conclusions: This study demonstrates that thioarsenicals, typified by $MMMTA^V$, downregulate the TCDD-mediated induction of CYP1A1, however further studies are required to explain the mechanism of this downregulation.

Support: This work was supported by Natural Sciences and Engineering Research Council of Canada (NSERC) Discovery Grant RGPIN 250139 to A.O.S.E. M.A.E. is the recipient of Antoine Noujaim Graduate Scholarship in Pharmaceutical Sciences.

Abstract H4 (oral presentation, poster not judged)

The role of the antioxidant enzyme NAD(P)H: quinone oxidoreductase-1 (NQO1) in toxicity mechanisms of clozapine.

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Purpose: The antipsychotic drug clozapine is the only medication for treatment-resistant schizophrenia. However, it is considered to be metabolized by neutrophils to electrophilic reactive metabolites including the clozapine nitrenium ion (CNI). The latter may generate oxidative stress and irreversibly damage critical neutrophil proteins, which may contribute to the dangerous side effect of agranulocytosis (potentially lethal neutropenia). The mechanism(s) for this toxicity are currently unknown but may involve modulation of phase II detoxifying enzymes. The level of quinone oxidoreductase (NQO)-2 has been reported to be low in clozapine-treated patients who developed agranulocytosis. Electrophilic reactive metabolites are known to induce expression of a closely related enzyme, quinone oxidoreductase-1 (NQO1), through the antioxidant response element (ARE). Since clozapine supposedly forms CNI, ***we hypothesize*** that clozapine/CNI induces NQO1 expression and activity.
Methods: HL-60 (human promyelocytic leukemia) cells are similar to neutrophil precursors and contain the enzymes needed to metabolize clozapine to the CNI, we used in this study. We investigated the effect of clozapine on enzymatic activity of NQO1 using selective substrates and inhibitors. We determined clozapine-induced NQO1 gene and protein expressions using RT-PCR and western blotting, respectively.
Results: Clozapine treatment induced concentration-dependent cytotoxicity (IC50≈48 μM, 48 h) in HL-60 cells. Also, a concentration-dependent increase of NQO1 activity, protein and mRNA level was found following 10–50 μM clozapine treatment. Treatment with 10 and 25 μM clozapine increased NQO1 activity to approximately two- and three-fold respectively in comparison to vehicle control. Moreover, about a two-fold rise in NQO1 protein and three-fold rise in NQO1 mRNA levels were accompanied in comparison to vehicle control.
Conclusions: The increase of NQO1 enzymatic activity and protein expression suggests clozapine induces a stress response. Further studies will be performed to determine if NQO1 induction is a protective mechanism against clozapine-induced cellular toxicity.

Abstract H5 (oral presentation, poster not judged)

Mechanisms Of Metabolism Interactions Between Mycophenolic Acid And P-cresol

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Purpose: Mycophenolic acid (MPA) is frequently used to prevent graft rejection after kidney transplantation. MPA is primarily metabolized by hepatic glucuronidation through UDP-glucuronosyltransferase (UGT) enzymes in the production of MPA-glucuronide (MPAG, major pathway) and MPA-acyl-glucuronide (AcMPAG). P-cresol is a microbiome-derived uremic toxin which can accumulate to relatively high plasma concentrations in patients with renal dysfunction. P-cresol has been shown to inhibit various glucuronidation enzymes. We hypothesized p-cresol is a potent inhibitor of MPA glucuronidation and this interaction is clinically significant.
Methods: The potency, mechanisms, inter-individual variabilities, and effects of clinical co-variates on the inhibitory effects of p-cresol toward the glucuronidation of MPA were characterized in human liver microsomes (HLM) and recombinant UGT enzymes at physiological concentrations. *In vitro-in vivo*

extrapolation were conducted to predict the exposure changes of MPA. Relative inhibitory effects of p-cresol compared to other common uremic toxins (e.g. indole-3-acetic acid, indoxyl sulfate, hippuric acid, kynurenic acid, 3-carboxy-4-methyl-5-propyl-2-furanpropionic acid) and its major metabolites (i.e. p-cresol sulfate and glucuronide) were also determined. Mechanisms of inhibition and kinetic constants were determined using model-fitting (SigmaPlot version 14). MPA, MPAG, and AcMPAG were measured by a liquid-chromatography tandem mass-spectrometry assay.
Results: P-cresol inhibited MPAG formation in a competitive manner (K_i=5.2μM), which was primarily mediated by UGT1A9. We predict an increase in MPA exposure by ~1.82-fold, which may lead to toxicity in patients, considering MPA's narrow therapeutic range. On the other hand, the mechanism of inhibition for AcMPAG formation was noncompetitive (K_i=127.5μM) and not clinically relevant. High inter-individual variabilities of p-cresol's inhibitory effects were evident and correlated to UGT1A9 enzyme activities. P-cresol was the most potent inhibitor compared to other uremic toxins and its metabolites.
Conclusions: Our novel findings indicated potent and clinically relevant inhibitory effects of p-cresol toward MPA glucuronidation. Further clinical experiments are on-going to verify our findings in humans.

Abstract H6
Heat–Stress Stability Of CBD Oils Analyzed By EPR Spectroscopy
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Purpose: The shelf life and stability of food oils has been analyzed previously by determining the peroxide content of the lipid peroxidation products. Oils, especially those which have unsaturated bonds, are considered easier to oxidize than oils which contain saturated fatty acids. Once peroxides are formed in oils, they can breakdown into free radicals, which can be harmful to the body. Oxidation can be catalyzed by exposure to heat, UV light, or metal contaminants. The importance of studying the stability of cannabis oils is to determine the longevity of the products such that rancidity and unwanted, potentially toxic byproducts can be discovered. The purpose of these studies is to: a) determine the breakdown of edible oils can be induced by exposure to heat, and b) to accurately determine if MCT (medium-chain triglycerides) oil can undergo breakdown and if APIs such as CBD or THC plays a role in the breakdown process. *Our hypothesis* is that cannabis products in MCT oil will breakdown slower than vegetable oils when exposed to the same heat-stress condition.
Methods: CBD and THC oil products from different companies were exposed to heat (50 °C/2 days). Oils were mixed with a spin-trap and catalyst and analyzed by EPR spectrometry.
Results: Free radical detection was observed in the positive control (aged sesame oil), whereas the vehicle control (MCT oil) showed no free radical signal. CBD 500 mg and CBD 1000 mg samples both indicated free radical detection but was significantly less intense than the positive control. Further studies using 5 different brands of THC oils indicated variable free radical content, which appeared related to the vehicle.
Conclusions: Preliminary data shows the importance of assessing the heat-stress stability of cannabinoid products since this can result in consumption of unwanted free radicals when consumed in a variety of ways.

Abstract H7
P-cresol-Induced Toxicity In HepaRG Cells
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Purpose: P-cresol is a uremic toxin that is mainly produced by anaerobic bacteria from amino acids in human intestine. P-cresol is accumulated to relatively high concentrations in plasma (i.e.>0.5mM) under uremic conditions, and is associated with liver, cardiovascular, and renal toxicities. P-cresol is primarily metabolized in the human liver forming p-cresol sulfate (PCS) and p-cresol glucuronide (PCG). We hypothesized that p-cresol can cause human liver injury by altering glutathione (GSH) homeostasis or by forming reactive metabolites.
Methods: HepaRG cells were differentiated and cultured following Biopredic's protocol. Concentration (0.25-2mM) and time-dependent-effects (0-24hr) of p-cresol on lactate dehydrogenase (LDH) release and GSH depletion were first determined. The relative effects of p-cresol compared to PCS, PCG, and other uremic toxins (e.g. indole-3-acetic acid, indoxyl sulfate, hippuric acid, kynurenic acid, 3-carboxy-4-methyl-5-propyl-2-furanpropionic acid) were characterized. GSH modulation using L-glutathione (3mM, to increase GSH) and L-buthionine sulfoximine (0.0625mM, to decrease GSH) were conducted. To probe the glucuronidation pathway, borneol (0.5, 0.75mM) was utilized as a non-specific and selective glucuronidation inhibitor. Concentrations of PCS and PCG were measured with liquid chromatography-tandem mass spectrometry assay from our lab.
Results: P-cresol increased LDH release at 0.5mM (EC_{50}=0.87mM) and decreased GSH at 0.75mM (EC_{50}=1.0mM) after 24hr-exposure. 1mM p-cresol evidently increased LDH release at 12hr and decreased GSH at 6hr. P-cresol was the most toxic compared to p-cresol's metabolites and other uremic toxins. L-glutathione decreased p-cresol-induced LDH release by 3.7%, while increasing GSH by 42.0%. Consistently, L-buthionine sulfoximine increased p-cresol-induced LDH release by 7.2% and decreased GSH by 100%. Borneol, at non-toxic concentrations (0.5, 0.75mM), inhibited PCG formation and significantly increased p-cresol-mediated LDH increase in a concentration-dependent manner.
Conclusions: P-cresol induces significant hepatotoxicity at concentrations attainable under uremia. GSH homeostasis does not appear to contribute to the toxicity and glucuronidation appears to be a detoxification pathway. Further mechanistic tests are ongoing.

Abstract I1

A Multifaceted Approach to Study Binding Modes of Tyrosine Kinase Inhibitors to hERG Cardiac Ion Channel

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Purpose: Cardiovascular complications as a result of cancer therapy is a growing challenge for many health care systems. This rising concern is also reflected in the drug development arena as the frequent emergence of cardiotoxicity from many approved anticancer treatments led to either discontinuing their use or, in some cases, their withdrawal from the market. A profound example is the class of tyrosine kinase inhibitors (TKIs), where there is a desperate and unmet need for strategies to eliminate their off-target cardiotoxic effects. However, the mechanisms for their induced cardiotoxicity are not fully understood and are relatively unexplored. Here we focused on understanding the mechanism of interaction of several TKIs with the hERG channel by combining multiscale molecular modelling and biochemical experiments.
Methods: The modeling workflow employs various in silico structure-based approaches and provides qualitative and quantitative insights into TKIs binding to hERG at the molecular level.
Results: The eight TKIs, gefitinib, lapatinib, sunitinib, vandetanib, crizotinib, nilotinib, ruxolitinib, vemurafenib, were tested in comparison to the standard E-4031 ($IC_{50} \approx 115$ nM) and were shown to possess varying levels of activity, ranging from IC_{50} of ~8.6 to 159.1 μM in a hERG fluorescence polarization assay. The modeling protocol helped us differentiate the structurally similar analogs and understand the binding mechanism of these compounds to the hERG channel. The structural analyses also indicate that the changes

in the structural networks and the disruption of the native π-π network present in the channel lead to their varying activities against hERG.
Conclusions: The combined results of these two interrelated methodologies provide a comprehensive understanding of the cardiotoxic mechanism of action of TKIs and sheds light on the various drug structural properties in order to reduce their cardiotoxic effects.

Abstract I2

Atomistic modeling of the human CaV1.2 channel: structural and mechanistic insights of cardiac ion permeation

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Purpose: Human CaV1.2 (hCaV1.2), a calcium selective voltage-gated channel, plays important roles in normal cardiac functions. Dysfunctions of CaV1.2 are related with multiple cardiovascular diseases, such as vasodilation, angina, and hypotension. Thus, understanding the structure-functiondynamics relationships of CaV1.2 is important to avoid and develop treatments of these diseases. Several small molecules (e.g. dihydropyridines and phenylalkylamine) have been identified and designed to modulate the activity of CaV1.2. Yet, their mode and site of action within the CaV1.2 channel are still unclear. This work focuses on building atomistic hCaV1.2 model and studying calcium channel blockers using computational approaches.
Methods: Toward this goal, this study employed computational molecular modeling techniques to model the transmembrane a1-subunit three-dimensional (3D) structure of the open and closed CaV1.2 channel. We used a combination of homology modeling and threading approaches along with classical and advanced molecular dynamics simulations to explore the conformational transitions between the closed and the open states of the channel. The ultimate goal was to predict the binding orientation and critical interactions for known CaV1.2 modulators.
Results: We report a comprehensive three-dimensional model of a closed state hCaV1.2 refined under physiological membrane-bound conditions using MD simulations. Our SMD simulations on the model revealed many conformational changes in the pore and voltage-sensing domains of the CaV1.2 channel. The mode-of-binding of dihydropyridines and phenylalkylamine were also identified to the atomic level. Our binding affinity calculations suggest that both dihydropyridines and phenylalkylamine have a high potential to block the CaV1.2 channel.
Conclusions: Our results have provided some important mechanistic insights into the structure, dynamics and ion permeation in hCaV1.2. The conformational dynamics and the interactions reported from our binding mode analysis will be useful for understanding the structure-function-dynamic relationship in the CaV1.2 channel and guiding future drug design efforts.

Abstract I3

Investigating the mode of action of a human B7-1 small molecule inhibitor: A computational study

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Purpose: Human B7-1 (CD80) is a member of the B7 family, which plays a key role in regulating T-cell function. B7-1 is normally expressed as a homodimer on the surface of antigen-presenting cells. It interacts

with two T cell receptors, namely CD28 and CTLA-4 to deliver co-stimulatory and co-inhibitory signals, respectively. B7-1 can also interact with PD-L1 to inhibit T cell activation. Since B7-1 is involved in different immunoregulatory functions, it has been considered as an important immunotherapy target, leading to the discovery of several B7-1 small molecule inhibitors. However, neither the sites nor the modes of binding for these molecules were clearly characterized. In this project, we aim to use computational modeling tools to investigate the binding site(s) and mode(s) of action of a potent B7-1 small molecule inhibitor.

Methods: We modeled the B7-1 protein in both monomer and homodimer states after adding a missing c-terminal domain and glycans. The two models were solvated in a TIP3P water box and Na^+ and Cl^- ions were added to achieve an electrostatically neutral environment. The solvated systems were energy minimized and equilibrated. Up to 100ns molecular dynamics (MD) simulations were performed to obtain stable conformations of B7-1. Clustering analysis was then performed to select representative conformations for docking analysis. Flexible docking was then used to identify the most probable binding locations and modes of binding of the B7-1 inhibitor.

Results: Based on our MD simulations, the B7-1 dimer showed more stability than the monomer. Potential binding poses of inhibitor:B7-1were also identified showing low binding energy and physicochemical complementary.

Conclusions: Through this project, the B7-1 models were established. MD simulations and docking analysis identified the most probable mode of binding of the small molecule B7-1 inhibitor. Further analysis, including free energy calculations on the generated complexes are required to confirm these findings.

Abstract I4

Developing a complete physiological model of the CTLA-4/B7-1 complex

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Purpose: Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) is a major immune checkpoint. The binding of CTLA-4 with the cognate B7-1 ligand expressed on antigen presenting cells delivers a signal that inhibits T cell activation, which has been discovered as an important mechanism exploited by cancer cells for immune evasion. Therefore, there is an enormous interest in developing inhibitors of CTLA-4/B7-1 interactions for cancer immunotherapy. But achieving this goal remains challenging, due to the lack in complete understanding of CTLA-4/B7-1 interactions. Most prior studies on CTLA-4/B7-1 have focussed only on the surface interactions of their extracellular domains. However, it is known that glycosylation and lipid interactions could have significant allosteric effects on stabilizing the CTLA-4/B7-1 complex. The objective of this work is to build the first computational model that will accurately describe all the physiological components present in the CTLA-4/B7-1 complex.

Methods: The transmembrane and intracellular domains of CTLA-4 and B7-1 were modelled using molecular modelling approaches. High mannose glycans were attached to the glycosylation sites on CTLA-4 and B7-1; and the complex was embedded in two lipid bilayers (one for each protein type). Additionally, we built two separate models of CTLA-4/B7-1 complex without the glycans and without the lipid layers to capture the effects of these components.

Results: In this work, we have successfully constructed the first complete near physiological model of the CTLA-4/B7-1 complex, which was equilibrated in a series of molecular dynamic (MD) simulations.

Conclusions: We have presently identified stable conformations of the whole CTLA-4/B7-1 complexes, with and without glycans and lipid layers. Further extended MD simulations of the complexes are required to analyze the effects of glycans and lipid contributions in stabilizing this complex. When completed, this

work will provide novel insights into the molecular basis of CTLA-4/B7-1 interactions, which should be useful for developing more potent inhibitors.

Abstract I5

Assessing the efficacy of τ-Random Acceleration Molecular Dynamics as a method for screening inhibitors of the hERG channel

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Purpose: The human *Ether-à-go-go*-Related Gene (hERG) channel is primarily known for its role in maintaining normal heart rhythm. hERG is also a mediator of proliferation in cancer cells, making it a novel target for cancer treatment. A major issue concerning hERG is its promiscuous interactions with diverse small molecules, leading to off-target interactions with various drugs. Although *in vitro* assays are available to screen for potential inhibitors, they are often expensive and time-consuming. This has led to the development of computational screening methods, which can offer a more cost-effective means of evaluating inhibitors. The purpose of this project is to assess the efficacy of a computational method, namely τ-random acceleration molecular dynamics (RAMD), in predicting the relative strength of hERG inhibitors.
Methods: We modeled six compounds with known residence times in complex with hERG. After minimization, heating, and equilibration, 10 ns of production simulations were performed to obtain stable bound-state conformations for each model. The VMD clustering tool was then used to extract the three dominant conformational clusters with the most frames throughout the production trajectories. 10 RAMD dissociation trajectories were then run for each replica to force ligand expulsion. Lastly, a bootstrapping procedure was performed on each compound to calculate their residence times in complex with hERG.
Results: When the computational residence times for the six compounds were compared to the experimental values, the R^2 was 0.7859, indicating a good correlation between the two data sets. Furthermore, when the most prominent outlier, Clofilium, was omitted from the analysis, the correlation increased to a R^2 of 0.8698.
Conclusions: This project suggests that τ-RAMD may be a viable means of screening for hERG inhibitors. Further analysis of the trajectories can provide insight into the specific chemical characteristics that promote affinity to hERG, allowing for more comprehensive screening in the future.

Abstract J1

Best practices in geriatric pharmacy education: An international survey of exemplars

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Purpose: While geriatrics is currently offered to some extent in most pharmacy curricula to prepare students to provide care for older adults, there is a lack of understanding of how geriatrics can be taught most effectively. This study aims to identify successful practices in teaching geriatrics in pharmacy curricula that could be adopted by other pharmacy schools.
Methods: Qualitative methodology was used. Subjects were identified through a network of geriatrics teaching organizations and colleagues internationally who identified exemplars in pharmacy education for geriatrics. These individuals were contacted by email. Data was collected using online surveys and semi-structured interviews. Participants were invited to provide background information and short answers to survey questions prior to interviews. Participants were asked about personal qualities, supports, teaching

and assessment methodologies, and challenges. Interviews were audio-recorded and transcribed for coding and thematic analysis.
Results: Eleven exemplars from Canada, USA, Australia, and Qatar participated in the study. They had a mean of over six years of teaching geriatrics courses. The main themes identified related to educator characteristics, practices, structures and policies, and challenges. Educator characteristics included passion in teaching and geriatrics, openness to innovative ideas, and commitment to lifelong learning. For practices, teachers described active discussions, hands-on simulations, interprofessional education, and research-informed teaching as effective strategies to engage students in active learning. For structures and policies, common facilitators included combinations of integrated and stand-alone geriatric component across curricula, increase of geriatric content and students' exposure to complexity of geriatric care, and comraderies within pharmacy faculty and with other professions. Challenges were described as packed curricula, complex topics, and ageism.
Conclusions: Exemplars in geriatrics education attributed their success in teaching to various personal, methodological, and contextual facilitators. Sharing successful experiences as well as lessons from challenges will allow pharmacy schools to move forward and advance geriatric education.

Abstract J2
Elucidating Sex Differences in the Pathogenesis of Diabetic Cardiomyopathy
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Purpose: Obesity is a major risk factor for diseases including type 2 diabetes (T2D) and cardiovascular disorders, particularly diabetic cardiomyopathy. Previous studies have indicated that the activity of pyruvate dehydrogenase (PDH), the rate-limiting-enzyme of glucose oxidation, is significantly reduced in diabetes via phosphorylation by PDH kinase 4 (PDHK4). Increased cardiovascular risk associated with diabetes is more noticeable in women, but an understanding of sex differences in augmentation of diabetic cardiomyopathy is lacking. Our aim was to elucidate the sex differences in glucose oxidation and insulin sensitivity in T2D/diabetic cardiomyopathy mouse model.
Methods: To address this, 6-week old C57BL/6J male and female mice were subjected to experimental T2D via high-fat diet (HFD) supplementation for 10-weeks, with a single injection of streptozotocin (75 mg/kg) at 4-weeks of HFD supplementation. Body weight and random blood glucose levels were assessed during diet intervention. At study completion, mice were euthanized, following which the heart and other peripheral tissues were extracted and evaluated for expression of genes/proteins involved in glucose homeostasis.
Results: Our data demonstrated that experimental obesity/T2D in male mice causes a greater increase in body weight and similar level of hyperglycemia than that in female mice. Moreover, gene expression profiling showed an increase in expression of *Pdk4* in the cardiac tissue of female mice. Concurrently, the expression of PDHK4 and phosphorylated PDH was increased in the cardiac tissue of female mice. Additionally, in the context of insulin sensitivity, our western blot data showed a reduction in the expression of phosphorylated protein kinase B and glycogen synthase kinase 3α/β in the cardiac tissue of female mice.
Conclusions: Our results in an experimental T2D/diabetic cardiomyopathy mouse model suggest that the heart of T2D females might have impaired insulin sensitivity and lower glucose oxidation rates than that in their male counterparts.

Abstract J3
Clinical relevance: Why are enteric coatings failing *in vivo*?
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Purpose: Over the last 70 years many cases of *in vivo* failure of enteric coated (EC) formulations have been reported. EC products present a marked slower dissolution in physiologically relevant buffer which seems to be the cause for the observed *in vivo* failures. Upon reaching the intestinal lumen, the dosage form is exposed to an environment buffered by bicarbonate at much lower molarities than those applied in compendial methods with phosphate buffer. The purpose of this work was to compare the *in vitro* performance of different marketed EC products and to elucidate the interaction between bicarbonate buffer (BCB) and enteric coating polymers.
Methods: The tested EC products included aspirin (Bayer Inc.), diclofenac sodium (Sandoz Canada Inc.), pantoprazole (Teva), esomeprazole (Apotex) and sulfasalazine (PMS). All dissolution tests were performed using an USP apparatus 2, 900 mL dissolution media, 75 rpm rotation speed and temperature set at 37.0°C. The tablets were tested in both phosphate buffer ~50mM pH 6.8 (except sulfasalazine: medium pH of 7.2) and BCB 5mM pH 6.5 after being exposed to HCl 0.1M for two hours.
Results: All formulations displayed a fast release in phosphate buffer and complied with the USP performance specifications. On the other hand, they all had a delayed drug release in BCB compared with that in phosphate buffer. The results clearly indicate that the *in vitro* performance of EC products is highly dependent on the ionic composition and molarity of the medium. In fact, this seems to impact the coat opening more than bulk pH. Consequently, in BCB, the generally accepted concept of a dissolution pH threshold for enteric coating polymers is questionable.
Conclusion: The physiological aspect of bicarbonate buffer should be taken into account during the formulation development process to avoid possible failures due to insufficient drug release.

Abstract J4

Ketones Can Become The Major Fuel For The Heart

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Purpose: Whether the heart orchestrates a metabolic adaptation to an increased ketotic milieu remains understudied. Therefore, our goal was to investigate how high levels of ketones (βOHB) affect the heart's function, efficiency and metabolic profile.
Methods: Isolated working mice hearts were aerobically perfused with radiolabeled palmitate (0.8mM), glucose (5mM) and increasing concentrations of βOHB (0, 0.6, 2.0mM). Subsequently, oxidation of these substrates, cardiac function and efficiency were assessed.
Results: Increasing βOHB concentrations increased myocardial ketone oxidation rates without affecting glucose or palmitate oxidation rates. Notably, ketones became the major fuel source for the heart at 2.0mM βOHB, contributing 66% of the heart's total energy production and increasing total cardiac energy production three-fold. Conversely, glucose and palmitate oxidation contributed 27% and 7% of the heart's total energy production, respectively. However, this unregulated increase in ketone oxidation as an energy source did not translate into an increase in cardiac work, and thus cardiac efficiency decreased when the heart was exposed to higher ketone levels.
Conclusions: Here we present novel observations demonstrating that ketones can become the major fuel source for the heart. Furthermore, ketones were not a more efficient source of fuel and increasing cardiac

ketone metabolism resulted in a decrease in cardiac efficiency. Our findings not only indicate that ketotic environments may negatively impact cardiac energetics but also underscore the importance of recognizing ketones as a major fuel source for the heart in times of starvation, consumption of a ketogenic diet or poorly controlled diabetes.

Abstract J5 (oral presentation, poster not judged)

Development of FOXM1 inhibitors as potential theranostic agents: initial steps in the validation of FOXM1 as a positron emission tomography (PET) probe for triple negative-breast cancer detection.

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Purpose: The FOXM1 transcription factor controls the expression of essential genes related to cell cycle progression and cell replication; under normal physiological conditions its expression is significantly decreased in terminally differentiated cells, but it is abnormally activated in most (if not all) malignant cells. During the last three years, our research group has worked on the development of novel (still experimental) FOXM1 inhibitors. We hypothesize that binding interactions exerted by FOXM1 inhibitors could not only inhibit its transcriptional activity but also serve as PET-based imaging probes, individually, ^{18}F-based imaging.

Methods: We prepared derivatives from **FDI-6**, (a drug reported back in 2014 by Gormally et al.,) and evaluated them as FOXM1 inhibitors by using the electrophoretic mobility shift assay (EMSA) method. To determine their ability to exert *in vitro* FOXM1 downregulation and anti-proliferative activity, we used a triple negative breast cancer cell line (MDA-MB-231). We selected derivative **FDI-AF** and designed a suitable method to radiolabel it with a Fluorine-18 atom, and prepared **^{18}F-FDI-AF** (radioactive analogue). We measured its cellular uptake in MDA-MB-231 cells, its metabolic stability, and in vivo tumor uptake in MDA-MB-231 tumor bearing mice.

Results: EMSA results showed that **FDI-AF** was able to dissociate the FOXM1-DNA complex with an IC_{50} = 46.4 ± 1.19 □M and Ki = 22.2 ± 0.56 □M, also exerted a downregulation of FOXM1 and inhibited cell proliferation in MDA-MB-231 cells (MTT assay, IC_{50} = 41.91 ± 1.20 □M). We prepared **^{18}F-FDI-AF** in 60% radiochemical yield, the cellular uptake results showed that **^{18}F-FDI-AF** is able to pass through the cell membranes as well as specificity towards FOXM1. In vivo study shows that **^{18}F-FDI-AF** is metabolically stable after one hour of its administration, however the *in vivo* tumour uptake results, showed a low uptake.

Conclusions: We have set the initial steps toward validating FOXM1 protein as target for PET imaging FOXM1 theranostic agents. These still preliminary results would lead to a better understanding on how to design FOXM1 inhibitors that are more suitable for PET imaging applications.

Abstract K1

Diabetes mellitus and myocarditis secondary to treatment with immune checkpoint inhibitors: a case report

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Background: Immune checkpoint inhibitors (such as nivolumab and ipilimumab) have been a recent advancement in the treatment of many cancers and have been shown to reduce mortality. While overall better tolerated than conventional chemotherapy, this class has unique immune-related adverse events (IRAE) which can present acutely and can be life-threatening. Several different toxicities have been

described involving the skin, respiratory, gastrointestinal, and endocrine systems. The exact mechanism of these toxicities is unknown but thought to be related to the development of autoreactive T cells.
Objectives: To describe an adverse drug reaction of diabetes mellitus and myocarditis after treatment with nivolumab and ipilimumab.
Case Description: A 68 year-old male with metastatic melanoma presented to hospital with diabetic ketoacidosis shortly after his second cycle of ipilimumab and nivolumab. He had a reduced level of consciousness and abnormal laboratory values (blood glucose 58.5 mmol/L, pH 6.92, anion gap 35 mmol/L). He was also found to have elevated troponins and an inflammatory injury on cardiac MRI consistent with myocarditis. He was discharged from hospital on insulin therapy, but fortunately did not have further cardiac complications.
Discussion: New-onset diabetes mellitus has been shown to have a prevalence of 0.9% in patients treated with this class of drugs. Patients who develop diabetes mellitus can experience a rapid course and diabetic ketoacidosis is a common presenting symptom. Myocarditis has been described to have a prevalence of 1.14% and may be associated with the development of major adverse cardiac events. IRAE occur more frequently when checkpoint inhibitors are used in combination.
Conclusions: While treatment with checkpoint inhibitors may improve survival, clinicians must be vigilant for the development IRAE. In this patient, he will likely require ongoing insulin therapy due to the development of diabetes secondary to nivolumab and ipilimumab treatment.

Abstract K2

Impact of Standardized Pharmacist-led Medication Teaching Videos on Patient and Clinician Experience

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Background: Island Health pharmacists process more than 160,000 orders per year for oral anticoagulants, common antihypertensives, beta-blockers and Statins. Subsequently, clinicians are inundated with the important time-consuming task of teaching patients about these medications, often leading to suboptimal knowledge translation and possibly taking clinicians away from other responsibilities. Video-based medical education has been shown to be as effective as traditional methods, allowing for information to be consistently delivered and reviewed. To offer a standardized and reproducible approach, videos featuring a pharmacist were developed for the aforementioned medications.
Objectives: To analyze the impact of implementing videos on patient and clinician experience, and to identify benefits and barriers to implementing videos in an acute care setting.
Methods: A survey-based quality improvement initiative was performed at Royal Jubilee Hospital from August 8 - October 4, 2019. Surveys were offered to patients discharged on one or more teaching video medications and to clinicians involved in administering videos.
Results: After watching the videos, all patient respondents reported they would recommend the videos to others, and 91.7% felt watching video(s) were better than a handout. 83.3% of patients reported feeling more confident in taking their prescribed medication(s) and an improved understanding of when to seek medical attention. Prior to implementation, 43% of clinicians reported spending 20-40 minutes on medication teaching, compared to 57% spending 10 or fewer minutes answering medication-related questions following video implementation. Clinicians identified video replay ability as a benefit whereas technical difficulties and video length as barriers to implementation.

Conclusion: Our survey results suggest videos reduce teaching time which may alleviate clinicians to perform other important activities without compromising medication teaching. Future work can be done to improve integration of videos into workflow.

Abstract K3

Beyond Bare Bones: Assessment of Patient Understanding After Attending an Inflammatory Arthritis Education Class

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Background: Inflammatory arthritis (IA) is a complex, chronic disease and patients must have a high level of disease competency. Patient education is recommended to supplement medical therapy, and is associated with clinical improvements. To meet these education needs, the Richmond Road Diagnostic and Treatment Centre Rheumatology Clinic offers a four-hour education session, *It's A Joint Effort*, for patients with IA.
Objectives: The aim of this study was to assess the impact of the education session on the patients' comprehension of IA and determine if the complexity and amount of information provided was appropriate.
Methods: Education class attendees completed an anonymous pre and post-session questionnaire.
Results: Over an 11-month period, 72 people participated in the quality assurance project. Four of the 72 survey responses were excluded because the participants did not complete both the pre and post survey sections. In 12 instances, single questions were excluded because of multiple or no response(s).
Prior to the session: 6.2% of participants either strongly agreed or agreed that they were familiar with the role of a social worker in the management of IA, 22% of participants indicated they strongly agreed or agreed that they were aware of ways to protect their joints and exercise safely, and 28.4% were familiar with resources to learn more about IA. After the session, responses for the same questions increased to 76.6%, 87.5%, and 83.6% respectively. The amount and complexity of the information was either agreed or strongly agreed to as being appropriate by 85.2% and 92.5% of patients respectively.
Conclusion: This survey suggests that the education session increased patients' knowledge and comprehension regarding the management of IA. Additionally, the complexity and amount of information provided was deemed appropriate.

Abstract K4

An Evidence Review and Comparison of the New IV N-Acetylcysteine Regimens for Acetaminophen Toxicity

Shawn Smith

Abstract K5

A Ketogenic Diet May Improve Weight Loss - a Review of the Literature

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Background: Recent popular interest has shifted from a low-fat diet to a low-carbohydrate diet, also known as a ketogenic diet, resulting in questions to community pharmacists regarding their comparative

efficacies for weight loss. A low-fat diet is accepted as dietary fat <30% of total daily caloric intake, whereas a ketogenic diet is ≤50 grams carbohydrates/day or <10% of total daily caloric intake.
Objective: To evaluate the literature regarding the efficacy and safety of a ketogenic diet, compared to a usual or low-fat diet.
Methods: A PubMed literature search was conducted for low carbohydrate or ketogenic diets with weight loss as an outcome of interest. Systematic reviews (SR) with meta-analyses and randomized controlled trials published after the most recent SR were reviewed and critically appraised.
Results: Two systematic reviews of moderate to high-quality showed significant improved weight loss, -2kg (range -0.17 to -3.4kg), compared to a low-fat diet. A recent randomized controlled trial demonstrated no difference in weight loss between a healthy low carbohydrate diet and a healthy low fat diet (-5.3kg vs -6.0kg) at one-year; carbohydrate intake ≤50g/day was not sustained; both diets had a similar range of weight loss (-30kg to 10kg) regardless of macronutrient intake; and overall caloric intake in both groups decreased by 20% at one-year. No specific adverse effects were noted with a ketogenic diet, however there was a significant increase of LDL, up to 0.16 mmol/L.
Conclusions: A ketogenic diet may improve weight loss up to 2kg when compared to a low-fat diet, but there appears to be poor long-term adherence to dietary carbohydrate restriction. Specific macronutrient restriction may not be as important as reduction in total caloric intake.