THE UNIVERSITY OF BRITISH COLUMBIA

Faculty of Pharmaceutical Sciences

2024 Faculty of Pharmaceutical Sciences Graduate and Postdoctoral Research Symposium

May 2, 2024, 8:00 am–4:30 pm

University Golf Club, 5185 University Blvd., Vancouver

Sponsored by fisher scientific

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Organizing Committee Members

Sina Halvaei, PhD candidate
Co-chair

Danielle Hanke,
PhD candidate
Co-chair

Thomas Chang,
Professor and Associate Dean, Graduate and Postdoctoral Studies

Caroline Liang, MSc student
Abstract and Program Co-lead

Vignesh Krishnamoorthy,
PhD student
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Abstract and Program Co-lead

Jacob Melamed, PhD student
Judging Co-lead

Tyler Thompson, MSc student
Judging Co-lead

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Angeline Wu, MSc student
Event Support Co-Lead

Acknowledgements

Land Acknowledgement

The 2024 Graduate and Postdoctoral Research Symposium is being held on the traditional, ancestral, and unceded lands of the xʷməθkʷəy̓əm (Musqueam) people. This area has always been a place of learning for the xʷməθkʷəy̓əm, and we feel privileged to have the opportunity to learn from our graduate and postdoctoral trainees and celebrate their research on this land during today's event. We hope you will take some time today to learn about the history of this land and to honour its original inhabitants. The resources at musqueam.bc.ca or indigenous.ubc.ca can help you get started. Acknowledging the land that we are situated on, and recognizing our role in the redress process, is an important part of our responsibilities as uninvited visitors on xʷməθkʷəy̓əm territory, and of the ongoing work required for reconciliation. We also invite you to identify, acknowledge and research the history of the lands you have come from, or are currently living and working on, by visiting the website native-land.ca.

Judges

Thank you to all our judges. This event wouldn't be possible without you!

Invited Speaker

Dr. Hila Behar: Co-founder and CEO of BryoSphere Biotechnologies

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Thank you to all our presenters and attendees!

Schedule

08:00–08:45 **Check-in, poster set up, continental breakfast**

08:45–08:50 **Welcome:** *Thomas Chang, Professor and Associate Dean, Graduate and Postdoctoral Studies*
Land Acknowledgement: *Danielle Hanke, GPRS Organizing Committee Chair*

08:50–08:55 **Opening Remarks:** *Sina Halvaei, GPRS Organizing Committee Chair*

08:55–09:55 **Podium Session 1:** MSc Student Presentations
Session Chair: *Noah Brittain*

08:55–09:07
A Decision-Tree Approach for Triacylglycerol Annotation of Data-Independent Acquisition-Based Lipidomics Data
Presenter: *Khanh Nguyen*

09:07–09:19
The Role of polySialic Acid in the Anticancer Immune Cell Response
Presenter: *Olivia Drummond*

09:19–09:31
Ambient Air Pollution Exposure and Adult Asthma Incidence: A Systematic Review and Meta-Analysis
Presenter: *Spencer Lee*

09:31–09:43
Pregnancy Outcomes of Targeted Synthetic and Biosimilar Disease Modifying Antirheumatic Drugs: A Scoping Review
Presenter: *Vienna Cheng*

09:43–09:55
Guideline-Concordant Inhaled Medication Use in COPD: A Systematic Review of Definitions Used in Administrative Health Data
Presenter: *Yiwei Yin*

09:55–10:05 **Transition/Biobreak**

Schedule – continued

10:05–11:05 **Poster Session 2:** Junior PhD Student Presentations
Session Chair: *Jonas Olsen*

10:05–10:17
Preclinical Evaluation of Polyamine Analogue, DENSpm, as a Targeted Therapeutic for Triple Negative Breast Cancer
Presenter: *Chloe White*

10:17–10:29
The Glyco-immune Checkpoint Receptor Siglec-7 Interacts with T-cell Ligands and Regulates T-cell Activation
Presenter: *Natalie Stewart*

10:29–10:41
Delivering Imiquimod using Phospholipid-Free Unilamellar Vesicles for the Treatment of Primary Liver Cancer and Liver Metastasis
Presenter: *Vanessa Chan*

10:41–10:53
Mental Health in People Living With and Beyond Colorectal Cancer: A Patient-Oriented Constructivist Grounded Theory
Presenter: *Vicki Cheng*

10:53–11:05
The Glycosyltransferase ST3GAL4 Drives Immune Evasion in Acute Myeloid Leukemia
Presenter: *Vignesh Krishnamoorthy*

11:05–11:20 **Coffee Break**

11:20–12:00 **Poster Session 3:** Senior PhD Student Presentations
Session Chair: *Jacob Melamed*

11:20–11:32
Drugging the "Undruggable": The Quest for Small Molecule Inhibitors of STAT Proteins
Presenter: *Danielle Hanke*

11:32–11:44
Exploring Sexual and Reproductive Health Among Adolescent and Young Adult Cancer Patients: A Patient-Oriented Qualitative Study Using Novel, Serial Focus Groups
Presenter: *Niki Oveisi*

11:44–11:56
Physiologically based Pharmacokinetic Model of Voriconazole for the Prediction of CYP3A4 mediated Drug-Drug Interactions
Presenter: *Sahithi Thotakura*

Schedule – continued

12:00–13:00 **Lunch**

13:00–14:00 **Co-founder and CEO of BryoSphere Biotechnologies**
Keynote Speaker: *Dr. Hila Behar*
Opening and Closing Remarks: *Danielle Hanke and Sina Halvaei*

14:00–14:05 **Transition/Biobreak**

14:05–15:05 **Podium Session 4:** Postdoctoral Fellow Presentations
Session Chair: *Chloe White*

14:05–14:17
Topical Drops for Enhanced Transdermal Delivery of Cosmeceutical Marcomolecular
Presenter: *Jiamin Wu*

14:17–14:29
Identification of Enolase1 as a Liquid Blood Biopsy Biomarker for Early-Stage Breast Cancer
Presenter: *Nikki Salmond*

14:29–14:41
Development of a Novel Polymer for Boosting Lipid Nanoparticle Delivery of Nucleic Acids
Presenter: *Ramya Kannan*

14:41–14:53
Restoring Biological Resilience in Epithelia Using Gene Therapy
Presenter: *Tiffany Carlaw*

14:53–15:05
Uncovering the Role of Long Non-Coding RNA Lnc-35682/PAN3-AS1 in Acute Myeloid Leukemia
Presenter: *Zhen Jin*

15:05–15:15 **Transition to Posters/Coffee Break**

Schedule – continued

15:15–16:05 **Poster Session 1: Junior MSc Student Poster Presentations**

15:15–15:23
Producing Novel Polymer-Based Lipid Nanoparticles for mRNA Delivery
Presenter: *April St Pierre*

15:23–15:31
Development of an Ultra-Rapid Magnetic Screening Method for Genetic Analysis of Cellular Glycosylation Pathways
Presenter: *Jimmy Kim*

15:31–15:39
Engineering Peptide Nanofibres to Optimize the Biointerface for Bacterial Encapsulation
Presenter: *Noah Brittain*

15:15–16:05 **Poster Session 2: Senior MSc Student Poster Presentations**

15:15–15:23
Implementation of Supervised Machine Learning Models to Predict Drug-Breastmilk Partitioning
Presenter: *Akash Panjabi*

15:23–15:31
Developing the Minipig for Use in Pharmacokinetic Modeling: Determination of Microsomal and Cytosolic Scaling Factors and Validation of NQO1/NQO2 Metabolism
Presenter: *Austin Zimmer*

15:31–15:39
Characterizing the Mechanism of Doxorubicin Mediated SAT1 Induction in Triple-Negative Breast Cancer
Presenter: *Caroline Liang*

15:39–15:47
The Effect of Changes in Social Ties on Waist Circumference in Aging Adults: Longitudinal Analysis of Canada's Aging Cohort
Presenter: *Rana Madani Civi*

15:47–15:55
Novel Therapeutic Targeting of CNOT3 in Acute Myeloid Leukemia
Presenter: *Renessa Gomes*

15:55–16:03
Lipid Nanoparticles Formulated in the Presence of 300 mM Sodium Citrate Enable Enhanced in vivo Gene Editing with CRISPR/Cas9 Adenine Base Editor mRNA and sgRNA
Presenter: *Tyler Thomson*

Schedule – continued

15:15–16:05 **Poster Session 3: PhD Student Poster Presentations**

15:15–15:23
A Discrete Choice Experiment of the Medication Preferences of People with Heart Failure: A Pilot Study
Presenter: *Blair MacDonald*

15:23–15:31
Design of Neutrophil-Inspired Antimicrobial Polyelectrolyte Nanocomplexes
Presenter: *Chinekwu Nwagwu*

15:31–15:39
Alcohol and Aldehyde Metabolism Gene Expression in the Minipig Liver
Presenter: *Maria Beletsky*

15:39–15:47
DYRK1b: A Novel Regulator of Extracellular Vesicle Dynamics in Breast Cancer
Presenter: *Sina Halvaei*

15:47–15:55
Phthalate Exposure and Placental Cell Lines; a Literature Review Comparing First and Term Like Placental Cell Lines with Exposure to DEHP and its Metabolites
Presenter: *Stuart Knight*

15:55–16:03
Rational Design of a Novel Adenosine Base Editor for Clinical Applications
Presenter: *Tessa Morin*

15:15–16:05 **Poster Session 4: Postdoctoral Fellow Poster Presentations**

15:15–15:23
Chemokine Receptor CCR7 Regulates Invadopodia Formation in Triple Negative Breast Cancer
Presenter: *Merlyn Emmanuel*

15:23–15:31
An Innovative Injectable Thermosensitive Hydrogel for Biomedical Applications
Presenter: *Tejinder Kaur*

16:05–16:15 **Coffee Break/View Posters**

16:15–16:18 **Door Prize Giveaway**

16:18–16:28 **Awards Ceremony**

16:28–16:30 **Closing Remarks**
Larry Lynd, Professor and Dean pro tem*, Faculty of Pharmaceutical Sciences*

Invited Speaker

Dr. Hila Behar
Co-founder and CEO of BryoSphere Biotechnologies

Opening & Closing Remarks: Danielle Hanke and Sina Halvaei

Hila Behar, Ph.D., is a passionate scientist and entrepreneur with a rich academic background and a deep love for science. Her journey began at Tel Aviv University, where she pursued a B.Sc. in Biology with aspirations for medical school. However, her passion for research took precedence, leading her to pursue a graduate degree in biochemistry and molecular biology. She continued her academic pursuit at the University of British Columbia, earning her Ph.D. from the Faculty of Medicine. During her time there, Dr. Behar made contributions to the field of plant biochemistry and protein characterization and enjoyed the academic mindset of curiosity and constant learning.

In April 2022, Dr. Behar co-founded BryoSphere Biotechnologies alongside Liz Mahon, a fellow UBC Ph.D. graduate. Drawing upon her academic experience, she discovered that the transition to entrepreneurship held many similarities to academia, leveraging relevant skills to drive innovation. At BryoSphere Biotechnologies, Dr. Behar is pioneering the development of moss as a biofactory for producing skincare ingredients. Her approach utilizes innovative tools from plant molecular biology to transform research findings into practical solutions for sustainable molecule manufacturing, making beneficial molecules more accessible.

Podium and Poster Presenters

MSc Student Podium Presentations

Khanh Nguyen
Olivia Drummond
Spencer Lee
Vienna Cheng
Yiwei Yin

Junior PhD Student Podium Presentations

Chloe White
Natalie Stewart
Vanessa Chan
Vicki Cheng
Vignesh Krishnamoorthy

Senior PhD Student Podium Presentations

Danielle Hanke
Niki Oveisi
Sahithi Thotakura

Postdoctoral Fellow Podium Presentations

Jiamin Wu
Nikki Salmond
Ramya Kannan
Tiffany Carlaw
Zhen Jin

Junior MSc Student Poster Presentations

April St Pierre
Jimmy Kim
Noah Brittain

Senior MSc Student Poster Presentations

Akash Panjabi
Austin Zimmer
Caroline Liang
Rana Madani Civi
Renessa Gomes
Tyler Thomson

PhD Student Poster Presentations

Blair MacDonald
Chinekwu Nwagwu
Maria Beletsky
Sina Halvaei
Stuart Knight
Tessa Morin

Postdoctoral Fellow Poster Presentations

Merlyn Emmanuel
Tejinder Kaur

MSc Student Podium Presentations

A Decision-Tree Approach for Triacylglycerol Annotation of Data-Independent Acquisition-Based Lipidomics Data

Presenter: Khanh Nguyen

Victor C.L. Lee[1], Khanh C.K. Nguyen[1], Linglan Zhu[2], Thomas J. Velenosi[1]

[1]Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, BC, Canada
[2]University of California Los Angeles, USA

BACKGROUND
Lipidomics analysis performed by data-independent acquisition (DIA)-based mass spectrometry enables the comprehensive detection of lipids, potentially maximize the number of identified lipids. However, the resulting spectra includes fragments from multiple co-eluting lipids, reducing lipid annotation confidence and limiting the adoption of this method. As the most abundant and diverse lipid class, triacylglycerol annotation is crucial but challenging. We aimed to develop a decision-tree based algorithm to annotate triacylglycerols in lipidomics data.

METHODS
Lipidomics data was acquired by LC-MS in MS^E DIA mode using liver and plasma samples from control and non-alcoholic fatty liver disease mice (NAFLD). A decision tree algorithm was created to annotate sample spectra with reference precursor and fragment ions. Annotations for triacylglycerols found were used to further refine species and molecular species level identification. To calculate an empirical false discovery rate (FDR), a decoy library of impossible triacylglycerol precursor and fragment combinations was generated, and a score was developed using a logistic regression model to rank putative target and decoy matches.

RESULTS
The intensity correlation matrix between fragment and precursor ions, the total number of missing fragments and precursors, the total intensity of fragments, and the dot product between fragment intensity were predictive of target matches. Using these four parameters, a logistic regression was applied to score target and decoy spectra matches. At a 10% FDR, we identified a total of 96 species and 756 molecular species of triacylglycerols in liver samples, and 75 species and 560 molecular species of triacylglycerols in plasma samples. A standard list of 9 common triacylglycerols was found at 9.3% and 5.0% FDR for liver and plasma samples, respectively.

CONCLUSIONS
A decision-tree based algorithm to systematically annotate spectra coupled with a decoy lipid library scored against known standards can improve the efficiency and confidence of triacylglycerol identification in DIA-based lipidomics analysis.

MSc Student Podium Presentations

The Role of polySialic Acid in the Anticancer Immune Cell Response

Presenter: Olivia Drummond

Olivia Drummond[1], Karla Williams[1], Simon Wisnovsky[1]

[1]*Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, BC, Canada*

BACKGROUND
In the breast cancer microenvironment, tumor infiltrating leukocyte cells can play a crucial role in eliciting tumor cell death. Most immunotherapies stimulate the anticancer activity of cytotoxic T-cells. Previously, we have identified the prognostic significance of the glycan polymer polysialic acid (polySia) on infiltrating immune cells in breast cancer patients. PolySia regulation or function in the human immune system has not been researched in depth, and further studies are required to understand how Polysia regulates the anticancer activity of cytotoxic T-cells.

METHODS
The profiling of polysialic acid on immune cell subsets is primarily done by flow cytometry. To identify proteins that are polysialylated on activated T-cells, I will use western blot and IP. I will conduct functional assays to assess the role of polysialic acid regulating immune activation and anticancer function. Depending on cell type, these will include cancer cell killing assays, proliferation assays and cytokine secretion assays.

RESULTS
I performed extensive immunophenotyping of polySia expression in immune cell subsets. Monocytes and naïve T-cells did not express polySia. However, stimulated T-cells express polysialic acid at high levels after one week of activation. The expression of polySia decreases at two weeks. In T-cells, Ncam is found to be polysialylated. Further studies will determine if polySia plays a role in the function of immune cell killing of cancer cells, such as phagocytosis or T-cell cytotoxicity.

CONCLUSIONS
Immunotherapy works to restore anti-tumor immunity and has become a new approach for breast cancer. Our work implies that polySia may be an inhibitory marker that restrains T-cell function and can be targeted for immunotherapy. My work will expand on the essential role that glycans play in anticancer immune cell function, with a specific focus on polysialylation.

MSc Student Podium Presentations

Ambient Air Pollution Exposure and Adult Asthma Incidence: A Systematic Review and Meta-Analysis

Presenter: Spencer Lee

Spencer Lee[1], Derek Tian[2], Jacquelyn J. Cragg[1,3], Chris Carlsten[4,5], Amanda Giang[6], Prubjot Gill[7], Kate M. Johnson[1,4,5], Emily Brigham[4,5]

[1]Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, British Columbia, Canada
[2]Faculty of Land and Food Systems, University of British Columbia, Vancouver, British Columbia, Canada
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[4]Division of Respiratory Medicine, Faculty of Medicine, University of British Columbia, Vancouver, British Columbia, Canada
[5]Legacy for Airway Health, Vancouver Costal Health Research Institute, Vancouver, British Columbia, Canada
[6]Institute for Resources, Environment and Sustainability, Department of Mechanical Engineering, Faculty of Applied Science, University of British Columbia, Vancouver, British Columbia, Canada
[7]Woodward Library, University of British Columbia, Vancouver, British Columbia, Canada

BACKGROUND
Exposure to higher concentrations of ambient air pollutants, are well-defined as risk factors incident childhood asthma. However, the impacts of ambient air pollutant exposures on the risk of incident adult asthma are less clear.

METHODS
A systematic review was conducted to assess the relationship between components of ambient air pollutant exposure ($PM_{2.5}$, NO_2, O_3, and SO_2), and incident adult (≥18 years) asthma. Studies were identified from Medline, Embase, Cochrane Central Register of Controlled Trials, and Web of Science from inception to September 2023 according to a registered protocol (PROSPERO: CRD42023420139). Study quality was evaluated using the Newcastle-Ottawa Scale. Meta-analysis was conducted using a random-effects model for exposure to individual ambient air pollution components and incident adult asthma. To evaluate factors that may contribute to heterogeneity, meta-regression was performed using study region, sex/gender, case definition of asthma, baseline pollutant exposure concentration, and co-pollutant adjustment.

RESULTS
Twenty-seven studies were included, addressing the following pollutants: $PM_{2.5}$ (n = 19), NO_2 (n = 18), O_3 (n = 4), SO_2 (n = 1). Meta-analysis was conducted for $PM_{2.5}$ (n = 9), NO_2 (n = 9), and O_3 (n = 4). The pooled random effects RR, for the outcomes of incident adult was 1.07 (95% confidence interval (CI): 1.01–1.13) per 5 μg/m^3 increase in $PM_{2.5}$ and 1.11 (95% CI: 1.03–1.20) per 10 μg/m^3 increase in NO_2. However, no significant pooled RR was found for O_3. Heterogeneity was substantial across all pooled effect size estimates (I^2 = 88), with baseline exposure level significantly contributing to heterogeneity for the pooled NO_2 estimate ($p<0.01$, I^2 = 26.8%).

CONCLUSIONS
Results add to the causal evidence base, supporting exposure to higher ambient $PM_{2.5}$ and NO_2 concentrations as a risk factor for incident adult asthma.

MSc Student Podium Presentations

Pregnancy Outcomes of Targeted Synthetic and Biosimilar Disease Modifying Antirheumatic Drugs: A Scoping Review

Presenter: Vienna Cheng

Vienna Cheng[1], Ursula Ellis[2], Mary De Vera[1]

[1]Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, BC, Canada
[2]Woodward Library, University of British Columbia, Vancouver, BC, Canada

BACKGROUND
Autoimmune rheumatic diseases disproportionately affect females more than males, and often strike during their reproductive years. Treatment is often necessary throughout the perinatal period and families are faced with the difficult challenge of weighing its risks and benefits. Recent emergence of targeted synthetic (ts) and biosimilar (bs) Disease Modifying Antirheumatic Drugs (DMARDs) has marked a revolutionary leap in autoinflammatory condition control. However, limited evidence on maternal-fetal risk presents a challenge for providers and families every day. We aimed to respond to this urgent need by synthesizing evidence on the perinatal impacts of these ground-breaking therapies.

METHODS
We conducted a scoping review following the Arksey and O'Malley framework(1). We searched for observational studies that examined maternal exposure to ts/bsDMARDs during pregnancy or paternal exposure ≤1 year preconception with a chronic autoinflammatory condition.

RESULTS
Of 6,716 studies screened, 167 were eligible for inclusion among 151,650 participants published between 2011 to 2023. Out of these, only 2 studies (1%) examined paternal exposure, with case reports accounting for 64% of the overall study designs. Most studies were published in 2022 (24%) and 2021 (17%). Subjects were mostly exposed to ustekinumab (13%) and tocilizumab (10%), both of which are interleukin inhibitors approved by Health Canada in 2008 and 2010, respectively. Inflammatory bowel disease (26%) and rheumatoid arthritis (14%) were the most prevalent conditions. Outcomes evaluated include those in the mother (e.g., gestational diabetes, placental abruption) and in the baby (e.g., stillbirth, congenital anomalies, low birth weight).

CONCLUSIONS
To our knowledge, this is the largest and first comprehensive synthesis of perinatal evidence on ts/bsDMARDs. Our findings bear profound implications that equip providers and families with a comprehensive understanding of these therapies on pregnancy, allowing the mitigation of fetal risks for all.

(1) Arksey, H., O'Malley, L. Scoping studies: towards a methodological framework. Volume 8, 2008.

MSc Student Podium Presentations

Guideline-Concordant Inhaled Medication Use in COPD: A Systematic Review of Definitions Used in Administrative Health Data

Presenter: Yiwei Yin

Yiwei Yin[1], Valerie Mok[2], Jaden Jeong[1], Emily Brigham[3,4], Mary A. De Vera[1], Mohsen Sadatsafavi[1], Kevin I. Duan[3,4,5], Kate M. Johnson[1,3,4]

[1]Collaboration for Outcomes Research and Evaluation, Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, British Columbia, Canada
[2]Faculty of Medicine, University of British Columbia, Vancouver, British Columbia, Canada
[3]Division of Respiratory Medicine, Faculty of Medicine, University of British Columbia, Vancouver, British Columbia, Canada
[4]Legacy for Airway Health, Vancouver Coastal Health Research Institute, Vancouver, BC, Canada
[5]Division of Pulmonary, Critical Care, and Sleep Medicine, University of Washington, Seattle, Washington, USA

BACKGROUND
Assessments of guideline-discordant use of maintenance inhaled therapies for chronic obstructive pulmonary disease (COPD) using administrative health data are common, but can be limited by the absence of detailed patient characteristics. We systematically reviewed definitions of guideline-concordant and guideline-discordant maintenance inhaled medication use that have been applied to administrative health data.

METHODS
We searched Medline and Embase from January 2000 to August 2023 for studies 1) used administrative health data to identify adults with COPD who were prescribed long-acting bronchodilators (LABDs) and inhaled corticosteroids (ICS) for outpatient treatment; 2) defined maintenance inhaled medication use as guideline-concordant and/or guideline-discordant at the patient-level.

RESULTS
We screened 3,960 records and included 17 studies. We identified 18 unique definitions. All definitions were based on the Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommendations. The most commonly measured definitions were 1) guideline-discordant ICS use (n=10), 2) guideline-concordant LABDs use (n=7), and 3) guideline-concordant ICS use, focusing on either ICS alone (n=4) or combined with LABDs (n=6). Seventy percent of studies measuring guideline-discordant ICS use and guideline-concordant LABDs use were consistent within the subset of the population described by the GOLD. However, no definitions for measuring guideline-concordant ICS use, whether focused on ICS alone or combined with LABDs, aligned with GOLD.

CONCLUSION
Definitions of guideline-concordant LABDs use and guideline-discordant ICS use in administrative health data are largely congruent with GOLD. However, studies only assessed a subset of the population included in GOLD recommendations due to the absence of clinical details in administrative data.

Junior PhD Student Podium Presentations

Preclinical Evaluation of Polyamine Analogue, DENSpm, as a Targeted Therapeutic for Triple Negative Breast Cancer

Presenter: Chloe White

Chloe White[1], Caroline Liang[1], Thomas Velenosi[1]

[1]Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, BC, Canada

BACKGROUND

Triple negative breast cancer (TNBC) accounts for about 15% of all breast cancer diagnoses worldwide and has the highest mortality rate of all breast cancer subtypes. TNBC is characterized by a lack of targetable receptors. This project aims to target a rate-limiting catabolic enzyme, SAT1, in the polyamine pathway to treat TNBC. Polyamines are small cationic molecules important for cell growth and replication, that are frequently upregulated in cancer. In this study, we utilized a polyamine analogue and SAT1 agonist, DENSpm, alone or in combination with doxorubicin, to induce SAT1 expression, and deplete polyamines, ultimately inhibiting tumour growth in different TNBC tumour phenotypes.

METHODS

This study utilized patient-derived xenograft models and TNBC cell lines with low (TM96, MDAMB453), moderate (TM98, BT549), and high (TM99, MDAMB468) baseline expression levels of SAT. Ex vivo tumour slices and cells were treated with doxorubicin, DENSpm, or both drugs in combination. Changes in SAT1 expression and polyamines were measured via qPCR, and LC-MS, respectively. Cell viability changes were analyzed using an incucyte.

RESULTS

Treating MDAMB468 with 10μM DENSpm for 48h resulted in a significant ($p < 0.05$) reduction of cell growth. Treating TM99 tumours with DENSpm resulted in a 2.6-fold SAT1 induction and significant depletion of polyamines ($p < 0.05$). Combination treatment of BT549 cells with 1μM doxorubicin and 10μM DENSpm significantly ($p < 0.001$) reduced cell viability compared to treatment with either drug alone. Combination treatment of TM98 tumour slices resulted in a 2.7-fold increase in SAT1-generated diacetylspermine and a 61% depletion of polyamines at sub-therapeutic doxorubicin concentrations.

CONCLUSIONS

The results of this study indicate that high baseline SAT1 expressing TNBC tumours may be susceptible to polyamine depleting therapy using DENSpm, and moderate baseline SAT1 expressing TNBC tumours may be susceptible to polyamine depleting therapy using a combination of DENSpm and doxorubicin.

Junior PhD Student Podium Presentations

The Glyco-immune Checkpoint Receptor Siglec-7 Interacts with T-cell Ligands and Regulates T-cell Activation

Presenter: Natalie Stewart

Natalie Stewart[1], John Daly[1], Olivia Drummond-Guy[1], Vignesh Krishnamoorthy[1], Jessica C. Stark[2], Nicholas M. Riley[4], Karla C. Williams[1], Carolyn R. Bertozzi[2,3], Simon Wisnovsky[1]

[1]Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, BC, Canada

[2]Department of Chemistry & Sarafan ChEM-H, Stanford University, Stanford, California 94305, USA.

[3]Howard Hughes Medical Institute, Stanford, California 94305, USA.

[4]University of Washington, Department of Chemistry, Seattle, WA, 98195, USA.

BACKGROUND

Siglec-7 is a glycan-binding immune receptor that is emerging as a significant target of interest for cancer immunotherapy. The physiological ligands that bind Siglec-7, however, remain incompletely defined. In this study, we characterized the expression of Siglec-7 ligands on peripheral immune cell subsets and assessed whether Siglec-7 functionally regulates interactions between immune cells.

METHODS

Peripheral blood mononuclear cells (PBMCs) sourced from several human blood donors were subjected to staining with a recombinant Siglec-7-Fc protein precomplexed to a fluorescently labeled secondary antibody to assess Siglec-7 ligand expression using flow cytometry. LC-MS/MS and immunoblotting was performed to then visualize the types of glycans that served as the main ligands for Siglec-7 on PBMCs. Furthermore, a set of T cell proliferation and cytokine profiling assays were conducted to show that Siglec-7/CD43 binding regulates T cell activation

RESULTS

We found that disialyl core 1 O-glycans are the major immune ligands for Siglec-7 and that these ligands are particularly highly expressed on naïve T-cells. Densely glycosylated sialomucins are the primary carriers of these glycans, in particular a glycoform of the cell-surface marker CD43. Biosynthesis of Siglec-7-binding glycans is dynamically controlled on different immune cell subsets through a genetic circuit involving the glycosyltransferase GCNT1. Siglec-7 blockade was found to increase activation of both primary T-cells and antigen-presenting dendritic cells (DCs) *in vitro*, indicating that Siglec-7 binds T-cell glycans to regulate intra-immune signaling. Finally, we present evidence that Siglec-7 directly activates signaling pathways in T-cells, suggesting a new biological function for this receptor.

CONCLUSIONS

These studies conclusively demonstrate the existence of a novel Siglec-7-mediated signaling axis that physiologically regulates T-cell activity. Going forward, our findings have significant implications for the design and implementation of therapies targeting immunoregulatory Siglec receptors.

Junior PhD Student Podium Presentations

Delivering Imiquimod using Phospholipid-Free Unilamellar Vesicles for the Treatment of Primary Liver Cancer and Liver Metastasis

Presenter: Vanessa Chan

Vanessa Chan[1], Julie Lee[2], Haruka Takata[3], Nojoud Al Fayez[1], Chun Yat Ong[1], Yun Ching Chen[2], Tatsuhiro Ishida[3], Shyh-Dar Li[1]

[1]Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, BC, Canada
[2]Institute of Biomedical Engineering, National Tsing-Hua University, Hsinchu, Taiwan.
[3]Faculty of Pharmaceutical Sciences, Tokushima University, Tokushima, Japan.

BACKGROUND
There are 768,000 new cases of liver cancer and 730,000 deaths worldwide every year. Only 15% of the cases are operable, and the median survival is generally <1 year. Response to immune checkpoint inhibitors can result in durable and long-term cancer control, but due to the immunosuppressive microenvironment of liver cancers, patients are often non-responders. To counteract the immunosuppression, an immune-boosting drug called Imiquimod (IMQ) can be used. By using PFSUV, a lipid-nanoparticle, we can localize IMQ to the hepatocytes and specifically increase cytokine levels.

METHODS
Two different mouse models were used to assess the efficacy of PFSUV-IMQ. For the primary liver cancer model, HCA-1 cells were inoculated directly into the livers of C3H mice. On day 10, a single dose of 6 mg/kg Oxaliplatin was administered IP. PFSUV-IMQ, Free IMQ, or saline was then administered at 1 mg/kg IV on days 11, 13, 15, 17, 19 and 21. Tumours and lungs were harvested on Day 24. Tumour size was measured, and lung nodules counted. For the liver metastasis model, CT26 cells were inoculated directly into the livers of Balb/C mice. Oxaliplatin was given at 6 mg/kg IP on day 4 and then PFSUV-IMQ, Free IMQ or saline was given IV on days 5, 7, 9, 11, 13 and 15. Tumours were then harvested on Day 16 and measured for size, CD8+ T cell infiltration and percentage of apoptotic cells.

RESULTS
PFSUV-IMQ treatment significantly lowered the tumour burden in both models. In the liver metastasis model, increased CD8+ T cell infiltration and percentage apoptotic cells was seen in the tumours of mice treated with PFSUV-IMQ. A significant decrease in metastatic lung nodules was observed in the primary liver cancer model.

CONCLUSIONS
PFSUV-IMQ treatment can significantly lower tumour burden and control metastasis in two different mouse models of liver cancer.

Junior PhD Student Podium Presentations

Mental Health in People Living With And Beyond Colorectal Cancer: A Patient-Oriented Constructivist Grounded Theory

Presenter: Vicki Cheng

Vicki Cheng[1,2], Helen McTaggart-Cowan[3,4], Jonathan M. Loree[5], Rachel A Murphy[3,6], Mikaela Barnes[7], Haydn Bechthold[7], Norman Jansen[7], Mary A. De Vera[1,2,8]

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BACKGROUND
Current literature suggests an association between colorectal cancer (CRC) and mental disorders. However, gaps in understanding the lived mental health experiences of patients with CRC exist. This study aims to explore mental health experiences in patients with CRC across the phases of the CRC care continuum, from treatment to follow-up to beyond.

METHODS
We employed a patient-oriented constructivist grounded theory design and recruited English speaking participants ≥ 18 years, diagnosed with CRC within the last 10 years, residing in Canada. We collected data through semi-structured individual interviews using a guide co-constructed with patient research partners. Data collection and analysis were iterative, employed theoretical sampling, and culminated in a theoretical model.

RESULTS
28 participants diagnosed with CRC (18 females, 10 males), aged 18-63 years at time of diagnosis were interviewed, with representation across all CRC stages. There were 10 participants (36%) in treatment, 12 participants (43%) in follow-up, and 6 participants (21%) in the beyond phase. We constructed a patient-oriented theory illustrating the dynamic nature between one's self-identity and their mental health experiences across the CRC care continuum. Mental health experiences encompass emotional and cognitive-behavioural responses, which are expressed differently across phases. Mental health care experiences are also shaped by barriers, facilitators, and individual contextual factors, all of which influence their access to care.

CONCLUSIONS
Our theory provides insight into the mental health experiences of patients with CRC across phases of the CRC care continuum. Understanding patients' emotional and cognitive-behavioral responses and care experiences can help identify opportunities to integrate mental health into CRC care.

Junior PhD Student Podium Presentations

The Glycosyltransferase ST3GAL4 drives Immune Evasion in Acute Myeloid Leukemia

Presenter: Vignesh Krishnamoorthy

Vignesh Krishnamoorthy[1], John Daly[1], Jimmy Kim[1], Lidia Piatnica[1], Katie Yuen[2], Ly Vu[1,2], Simon Wisnovsky[1]

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BACKGROUND
Cancer cells often express aberrant levels of molecules containing sialic acid resides (sialoglycans) on their cell surface. These sialoglycans can bind to Siglec receptors expressed by immune cells and quench their cytotoxic activity. Studies have shown that blocking the interaction between cancer associated sialoglycans and the Siglec receptors can unleash the activity of immune cells against cancer cells and eliminate them. Siglec-9 is one such receptor expressed on the surface of myeloid cells. Demystifying the identify of Siglec-9 binding glycan ligands would allow to develop enhanced immunotherapeutic approaches against cancer cells.

METHODS
A CRISPR-Cas9 screen performed on a myeloid leukemia cell line identified the glycosyltransferase ST3GAL4 as a topic hit gene controlling the synthesis of Siglec-9 binding ligands. ST3GAL4 expression levels was analyzed in multiple cancer models. Acute myeloid leukemia (AML) cell lines were evaluated for the expression levels of Siglec-9 binding ligands through flow cytometry. ST3GAL4 was knocked out in multiple AML cell lines through CRISPR-Cas9 based approach. The WT/ ST3GAL4 KO cells were co-cultured with primary macrophages and the phagocytic index was calculated.

RESULTS
The mRNA expression levels of ST3GAL4 was high in AML cells compared to healthy blood cells. Flow cytometry analysis revealed that AML cells express high levels of Siglec-9 binding ligands. Loss of ST3GAL4 significantly reduced the expression levels of Siglec-9 binding ligands compared to the WT cells. Co-culture of WT/ST3GAL4 KO cells with primary macrophages revealed that the ST3GAL4 KO cells are more sensitive to phagocytosis compared to the WT.

CONCLUSIONS
Our studies indicate that the expression of Siglec-9 binding ligands on AML cells are controlled by ST3GAL4. Loss of ST3GAL4 in AML cells makes them more prone to phagocytic attack by macrophages. These results illustrate a novel checkpoint inhibitory pathway utilized by AML cells that could be exploited for developing effective immunotherapies.

Senior PhD Student Podium Presentations

Drugging the "Undruggable": The Quest for Small Molecule Inhibitors of STAT Proteins

Presenter: Danielle Hanke

Danielle Hanke[1], Melanie McDonald Lopez[2], David A. Frank[2], Brent D.G. Page[1]

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BACKGROUND
The Signal Transducer and Activator of Transcription (STAT) proteins are a family of proteins that are notoriously difficult drug targets, as they lack a traditional enzyme active site where small molecule inhibitors would typically bind. However, aberrant STAT activity is associated with cancers and inflammatory diseases, therefore inhibiting these proteins would open a breadth of possibilities for novel therapeutic agents. The STATs have been the target of many drug development pipelines, but all have been unfruitful in uncovering potent and selective STAT inhibitors. This research project employs innovative new strategies such as thermal stability assays to identify small molecule inhibitors that target STAT proteins directly.

METHODS
High throughput screens (HTS) were conducted on ~33 000 chemical compounds to search for direct inhibitors of STAT1 protein. Further thermal stability assay experiments were performed to validate promising hit compounds. Chemical optimization was conducted on top hits to synthesize a small library of compounds which were further tested in cellular assays to assess STAT binding and inhibition.

RESULTS
Three top hit compounds were identified from the initial HTS and validation experiments based on their ability to stabilize STAT1 towards thermal denaturing. These hits were diversified and optimized using medicinal chemistry techniques to create a library of ~80 chemical compounds for further biochemical testing. Six top compounds were chosen from these experiments and tested in cellular assays to assess their STAT inhibitory activity, where one compound (BP170) showed selective and potent STAT5 inhibition.

CONCLUSIONS
Discovering ways to target "undruggable" proteins such as the STATs will broaden the therapeutic horizon for many diseases. We hope that through mechanistic studies and further optimization of BP170 we will be able to develop an even more potent and selective STAT5 inhibitor that will have applications as a novel cancer therapeutic.

Senior PhD Student Podium Presentations

Exploring Sexual and Reproductive Health Among Adolescent and Young Adult Cancer Patients: A Patient-Oriented Qualitative Study Using Novel, Serial Focus Groups

Presenter: Niki Oveisi

Niki Oveisi[1,2], Vicki Cheng[1,2], Dani Taylor[3], Haydn Bechthold[3], Mikaela Barnes[3,4], Norman Jansen[3], Helen McTaggart-Cowan[5,6], Lori A. Brotto[7], Stuart Peacock[5,6], Gillian E. Hanley[7], Sharlene Gill[5,7], Meera Rayar[7], Amirrtha Srikanthan[8,9,10], Mary A. De Vera[1,2,11]

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BACKGROUND
Treatment advancements for adolescent and young adult (AYA, ages 15–39) cancers are improving survival rates, yet there's a lack of information and support for the impact on sexual and reproductive health (SRH). Our study delved into SRH experiences of AYA cancer patients through serial focus groups.

METHODS
We recruited individuals diagnosed with cancer between ages 15–39, residing in Canada, and over 18. Participants formed cohorts based on similar characteristics (e.g., sex, stage) and engaged in three focus groups each, mirroring support groups. An interview guide, developed iteratively with patient research partners, facilitated framework analysis to uncover recurring SRH themes.

RESULTS
We recruited 4 focus group cohorts, with 6–10 participants each (N = 24 females, 6 males), representing various cancer types and stages. Cohorts included transgender (n = 1) and gender-diverse folks (n = 3), non-heterosexual sexual orientation (n = 11), and racial diversity (n = 9). Three themes emerged: 1) internally ("looking inwards") – impact of AYA cancer on SRH; 2) externally ("looking outwards") – impact of cancer on interpersonal relationships; and 3) role of the healthcare system. Internally, folks described impacts of AYA cancer on themselves, revealing shifting definitions, expectations, and goals of SRH. Participants explained mental, physical, and financial changes that positively or negatively impacted SRH and influenced short and long-term well-being. Externally, changes in romantic relationships and family planning underscored the complex interplay of societal pressures on SRH and reproductive choices. Regarding the healthcare system, findings highlight facilitators (i.e., self-advocacy, nurses, recent pregnancy, etc.) and barriers (i.e., gender, SRH stigma, age, fertility treatment costs, heteronormativity, etc.) influencing access to appropriate and available SRH resources and support.

CONCLUSIONS
AYA cancer poses significant SRH challenges, impacting internal well-being and external relationships. Understanding these experiences can inform more effective integration of SRH care into the cancer care continuum.

Senior PhD Student Podium Presentations

Physiologically Based Pharmacokinetic Model of Voriconazole for the Prediction of CYP3A4 Mediated Drug-Drug Interactions

Presenter: Sahithi Thotakura

Sahithi Thotakura[1], Anil Maharaj[1]

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BACKGROUND
Voriconazole (VCZ) is a triazole antifungal agent indicated to treat fungal infections. VCZ is metabolized by multiple hepatic enzymes and exhibits high inter-individual variability due to pharmacogenetic variation of CYP2C19 and autoinhibition of CYP3A4. The latter not only alters the VCZ exposure with sustained dosing but also increases exposure of co-administered medications metabolized by CYP3A4. Owing to VCZ use in critical care settings, where patients receive multiple medications, an understanding of the extent of drug-drug interactions (DDI) perpetuated by VCZ is important to ensure patient safety. In this study we developed a physiologically based pharmacokinetic (PBPK) model for VCZ to predict CYP3A4 mediated DDI.

METHODS
The VCZ PBPK model was developed using in-vitro and in-vivo data. We leveraged the pharmacokinetic (PK) data from CYP2C19 pharmacogenetic studies to optimize clearance mediated through CYP2C19. Additionally, data from DDI studies involving prototypical CYP3A4 substrates (e.g., midazolam) were incorporated to optimize enzyme inhibition parameters and develop the final model. The final VCZ model is then used to predict potential DDI with other CYP3A4 substrates such as fentanyl.

RESULTS
Among the 48 datasets identified from 14 clinical studies, 17 datasets (35.4%) were allocated for model development, while the remaining 31 datasets (64.5%) were reserved for validation. Preliminary results from single-dose intravenous datasets (n=10) show that 90% of predicted area under the curve (AUC) and maximum concentration (C_{max}) are within 1.5-fold acceptance criteria. For single-dose oral datasets (n=7), 100% of predicted AUC and 85% of predicted C_{max} meet the 1.5-fold acceptance criteria. This model will further be used to optimize and predict DDI.

CONCLUSIONS
The developed VCZ model can be used to evaluate the DDI potential and determine dosage adjustments when VCZ is co-administered with other medications metabolized by CYP3A4, reducing the need for clinical trials to evaluate DDI.

Postdoctoral Fellow Podium Presentations

Topical Drops for Enhanced Transdermal Delivery of Cosmeceutical Marcomolecular

Presenter: Jiamin Wu

Jiamin Wu[1], Tejinder Kaur[1], Justin Huang[1], Shyh-Dar Li[1]

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BACKGROUND

The growing interest among consumers in achieving healthier-looking skin has highlighted the need for a reliable and safe method to enhance the absorption of large-molecule cosmeceuticals, including substances like hyaluronic acid (HA), collagen, and peptides through the skin. However, the natural barrier function of the outermost layer of the skin, known as the stratum corneum, limits the penetration of these large molecules.

METHODS

In this study, a needle-free system (novel cell penetrating peptides, CPPs) is introduced, which significantly improves the transdermal delivery of molecules up to 800 kDa in size. The effectiveness of this system in facilitating the penetration of large molecules is explored using both porcine skin and human skin substitutes. Additionally, a specialized human skin substitute model for psoriasis is utilized to evaluate the system's performance on thinner, more sensitive skin.

RESULTS

The results indicate a notable increase in the delivery of FITC-HA into the epidermis of porcine skin, with a twentyfold improvement observed within just ten minutes of application. Furthermore, experiments conducted on human skin substitutes demonstrate that the system enhances the delivery of FITC-HA by up to 68 μm and IgG by up to 70 μm. Furthermore, when applied to the psoriasis human skin substitute model, the system showed enhanced inhibition of keratinocyte differentiation when combined with an anti-interleukin 17A (IL-17A) antibody.

CONCLUSION

Overall, these findings suggest that the novel CPPs utilized in this system offer an effective and safe approach for the non-invasive delivery of cosmeceutical macromolecules such as HA and monoclonal antibodies.

Postdoctoral Fellow Podium Presentations

Identification of Enolase1 as a Liquid Blood Biopsy Biomarker for Early-Stage Breast Cancer

Presenter: Nikki Salmond

Nikki Salmond[1], Karan Khanna[1], Kelly Tam[1], Renata Moravcova[2], Jason Rogalski[2], Karla. C. Williams[1]

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BACKGROUND
The key to successful treatment and long term remission of breast cancer, is to diagnose it early. Approximately 80% of breast growths are benign, but current methodologies used for breast cancer diagnosis are unable to distinguish a benign versus cancerous breast mass, meaning that many unnecessary and invasive needle biopsies are carried out every year. We need a liquid blood biopsy—a routine blood test—to diagnose breast cancer in its earliest stages. We propose that extracellular vesicles (EVs)—tiny circulating tumor fragments—show great promise for the development of new diagnostic procedures because the contents of EVs reflect those of the parental cancer cell.

METHODS
Size exclusion chromatography was used to isolate EVs from 81 early stage breast cancer, 19 benign and 20 healthy plasma samples. Peptide mapping was done on 20 µg of each sample spiked with 200 fmol yeast glutathione reductase as a label-free quantification marker. Identified diagnostic biomarkers were validated in plasma using ELISA. Early breast cancer biopsy tissues were observed using immunohistochemistry. In-vitro experiments were done using MCF10A, MCF7 and MDA-MB-231 cells.

RESULTS
Mass spectrometry identified EV-associated Enolase1 as a predictive early breast cancer biomarker. Mass spectrometry data was validated using ELISA on plasma samples and this was able to distinguish breast cancer patients from individuals that were healthy or had a benign breast growth. Enolase1 localisation in tumor tissue matched to the plasma samples showed a diffuse localisation conducive with a secretory phenotype. Enolase1 expression, localisation and secretion was also investigated in breast cancer cell lines MCF7 and MDA-MB-231, and benign hyperplasia MCF10A cells.

CONCLUSIONS
Enolase1 is a promising plasma biomarker of early stage breast cancer. We are now developing a more sensitive and high-throughput method than ELISA for the analysis of breast tumor derived EVs using nanoscale flow cytometry.

Postdoctoral Fellow Podium Presentations

Development of a Novel Polymer for Boosting Lipid Nanoparticle Delivery of Nucleic Acids

Presenter: Ramya Kannan

Ramya Kannan[1], Quan Le[1], Sophie Roesger[1], Vivekjot Brar[1], Lukas Hohenwarter[1], Po-Han Chao[1], Angel Lee[2], Jing-Ping Liou[3], Shyh-Dar Li[1]

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BACKGROUND

Lipid nanoparticles (LNPs) have emerged as promising carriers for delivering nucleic acids. However, less than 2% of the payload is mostly being released in the cytosol by the LNP-mediated delivery.[1] To address this major barrier, we have synthesized a novel polymer (NS01) that can destabilize lysosomes and be incorporated within LNPs.

METHODS

In this study, we optimized LNP formulations by incorporating varying amounts of the NS01 polymer, and assessed their physicochemical properties such as particle size, polydispersity, and zeta potential. Further, their *in vitro* and *in vivo* transfection efficacy and efficiency were also tested.

RESULTS

The resulting polymer-incorporated LNPs exhibited physicochemical properties comparable to those of standard LNPs. The *in vitro* results of eGFP loaded polymer-incorporated LNPs displayed increased fluorescence intensity after 24 h in comparison with standard LNPs. Notably, the polymer-incorporated LNPs carrying a luciferase mRNA demonstrated a substantial increase (**~2 orders of magnitude**) in luciferase gene expression following intravenous (IV) and intramuscular (IM) injections, when compared to standard LNPs. Importantly, the polymer-incorporated LNPs displayed no *in vivo* toxicity when tested the for the serum levels of liver enzymes, including Alanine transaminase (ALT) and Aspartate transaminase (AST).

CONCLUSIONS

This study demonstrates that the NS01 polymer could be incorporated into various LNP formulations featuring different ionizable cationic lipids, yielding consistent and promising outcomes. The resulting formulation also serves as a proof of concept for incorporating similar class of polymers in traditional LNPs for improved transfection efficiency.

1. Francia V, Schiffelers R M., Cullis P. R., and Witzigmann D. The Biomolecular Corona of Lipid Nanoparticles for Gene Therapy. *Bioconjugate Chem.* 31, 9, 2046–2059 (2020)

Postdoctoral Fellow Podium Presentations

Restoring Biological Resilience in Epithelia Using Gene Therapy

Presenter: Tiffany Carlaw

Tiffany Carlaw[1], Dilem Apaydin[2], Belal Tafech[1], Vincent Halim[3], Tessa Morin[1], Jayesh Kulkarni[4], Pieter Cullis[3], Colin Ross[1], Eric Jan[3], Sarah Hedtrich[1,2]

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BACKGROUND
Inherited skin and lung diseases are a challenge for the development of gene therapy strategies in that they possess significant delivery barriers: the mucosal lining in lung and the outer dermal layers in skin. Recently, the Hedtrich lab has made significant strides to overcome these delivery barriers and are primed for the development of novel gene therapeutics. We selected two targets 1) autosomal recessive congenital ichthyosis (ARCI) a group of rare, inherited skin diseases and 2) cystic fibrosis, an inherited lung diseases caused by mutations in CFTR.

METHODS
We designed and employed CRISPR/Cas9 base editing strategies to correct pathogenic mutations for each target: TGM1 c.877-2A>G for ARCI skin disease and *CFTR*^{R1162X} for cystic fibrosis. For each mutation we obtained patient cell lines (human skin keratocytes and nasal epithelial cells) as models to evaluate and optimize gene editing. We then optimized our gene editing approach by testing novel base editor constructs, comparing modifications to the mRNA structure and comparing modifications to sgRNA stability.

RESULTS
We initially screened sgRNA designs, base editors and ratios of mRNA:sgRNA using Lipofectamine™ RNAiMAX. From these screens we selected the best sgRNA, base editors and ratios for each target. Next, we focused on TGM1 c.877-2A>G and compared different 5′ and 3′ untranslated regions (UTRs), improving our initial on-target editing efficacy, achieving 24% base editing. TGM1 c.877-2A>G mutation affects a 3′ splice acceptor site, for which the sequence is invariably "AG", placing a critical bystander nucleotide directly next to our target nucleotide. To overcome this, we next employed eTD-CBE and were able to achieve 35% editing at our target nucleotide and importantly minimal editing of the bystander.

CONCLUSIONS
The next steps in this project will be to combine the efforts of all previously optimization experiments with a therapeutically relevant delivery strategy using novel lipid nanoparticle formulations.

Postdoctoral Fellow Podium Presentations

Uncovering the Role of Long Non-coding RNA *Lnc-35682/PAN3-AS1* In Acute Myeloid Leukemia

Presenter: Zhen Jin

Zhen Jin[1,2], Maryam Ghashghaei[1,2], Kyle McPherson[2], Ly Vu[1,2]

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BACKGROUND
Acute myeloid leukemia (AML) is a heterogenous set of diseases exhibiting excessive abnormal myeloid cells, with a patient 5-year survival rate less than 30%. Despite advances, reducing morbidity remains difficult. Long non-coding RNAs (lncRNAs), transcripts over 200 nucleotides without protein coding potential, has recently emerged as an important class of regulators of tumorigenesis. Although over 160,000 human lncRNAs are identified, most are still unexplored. Understanding their functions could reveal new cancer treatment targets.

METHODS
By performing comparable transcriptome profiling, we de novo identified a murine lncRNA, *Lnc-35682*, that is expressed in mouse hematopoietic stem/progenitor cells but significantly upregulated in leukemia cells. Syntenic analysis revealed *PAN3-AS1* as the functional human homolog of *Lnc-35682*. To investigate the function of *Lnc-35682/PAN3-AS1* in leukemia, we performed loss and gain of- function analysis both *in vitro* and *in vivo* using mouse and human leukemia cells. A genetic mouse model of *Lnc-35682* germline knockout (KO) was generated to evaluate requirement of *Lnc-35682* during normal hematopoiesis. To explore the regulatory mechanisms of *PAN3-AS1* in AML, we employed transcriptome, proteome profiling, ATAC-sequencing, and iDRiP (identification of direct RNA interacting proteins) techniques. Lipid nanoparticles carrying siRNAs are being explored to target *PAN3-AS1* in AML.

RESULTS
We uncovered a novel lncRNA, *Lnc-35682/PAN3-AS1* that is elevated in AML cells, particularly in FLT3-ITD AML subtype. High expression of *PAN3-AS1* correlates with unfavorable prognosis in AML patients. Knockdown (KD) of *Lnc-35682/PAN3-AS1* significantly inhibited survival of both mouse and human leukemia cells *in vitro* and in xenografted mouse models. *Lnc-35682/PAN3-AS1* overexpression (OV) promoted leukemia cell growth. Genetically KO of *Lnc-35682* efficiently delayed leukemogenesis while sparing normal hematopoiesis. *Lnc-35682* OV rescued *PAN3-AS1*-KD human leukemia cell growth. Mechanistically, *PAN3-AS1* promotes its neighboring genes.

CONCLUSIONS
We identified a functionally conserved lncRNA, *Lnc-35682/PAN3-AS1*, that fuels leukemogenesis and represents a leukemia-specific-vulnerability which we can exploit for AML therapy.

Junior MSc Student Poster Presentations

Producing Novel Polymer-Based Lipid Nanoparticles for mRNA Delivery

Presenter: April St. Pierre

April St. Pierre[1], Feng Zhao[1], Ramya Kannan[1], Shyh-Dar Li[1]

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INTRODUCTION

Lipid nanoparticles are widely used in research, as well as in the Comirnaty and Spikevax COVID-19 vaccines, to deliver mRNA cargo and produce protein expression. These particles are typically made using four lipids: ionizable lipid, PEG-lipid, cholesterol and a helper lipid such as DSPC[1]. Particles made with this composition have limited ability to effectively target extrahepatic tissues in vivo, and also face the challenge of low endosomal escape which decreases their potency[1]. To address these challenges, we propose using novel polymers developed in the Li lab, along with other lipids, to produce lipid nanoparticles with a novel composition. These novel particles will have enhanced potency due to the incorporation of the novel polymer, which has been found by the Li lab to increase endosomal escape. They may also reach extrahepatic tissues more effectively due to their novel composition.

METHODS

Particles composed of a novel biodegradable polymer, corn oil, tween80 and phospholipids, as well as mRNA, were made by T-mixing. These particles were optimized by altering the ratios of the components to obtain desired size, PDI, and encapsulation efficiency. Particles were then tested for their ability to transfect cells and induce protein expression.

RESULTS

Particles below 90nm in size were successfully formed and found to encapsulate mRNA. Luciferase protein expression was detected after treatment with these nanoparticles.

CONCLUSIONS

This project shows that lipid nanoparticles can be made from a novel combination of lipids, and that these particles can be used to induce protein expression with mRNA. In light of these results, further study of these particles as a drug delivery method should be carried out.

1. Hou, X., Zaks, T., Langer, R. & Dong, Y. Lipid nanoparticles for mRNA delivery. *Nat. Rev. Mater.* **6**, 1078–1094 (2021).

Junior MSc Student Poster Presentations

Development of an Ultra-Rapid Magnetic Screening Method for Genetic Analysis of Cellular Glycosylation Pathways

Presenter: Jimmy Kim

Jimmy (Jongyoon) Kim[1], Simon Wisnovsky[1]

[1]*Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, BC, Canada*

BACKGROUND
In 2018, the Nobel Prize in Medicine recognized the groundbreaking potential of cancer immunotherapies, drugs that allow the immune system to target and eliminate cancer cells. The human immune system functions by utilizing receptors expressed on the surface of immune cells. Upon binding to specific targets (ligands), these receptors result in a decrease in immune response. In diseases like cancer, the cell surface may be altered to overexpress certain ligands, leading to suppression of immune cell activity and immune evasion. The signaling pathways and genetic changes that modify the cell surface in cancer cells, however, are not well defined. If these regulators could be identified and characterized, this could open doors to the development of targeted immunotherapeutics that act by remodeling the cancer cell surface.

METHODS
My lab has developed a genome-wide screening method that aims to uncover these regulators. One downside of this screening method, however, is the flow-based sorting component of the workflow, which is very time-consuming (~10 hour experiments) and not well-suited to cell lines that are difficult to sort (e.g., adherent, epithelial cancer cell lines). I aim to develop and apply an improved magnetic-sorting method to map pathways underlying cancer hypersialylation in a wider range of cell models.

RESULTS
I optimized the conditions for efficient separation, then conducted a genome-wide screen with MDA-MB-231 (breast cancer) cells and identified genes involved in sialic acid biosynthesis (CMAS, GNE, ST8SIA4), as well as potential oncogenes of interest (CD44, ILKAP2, EDA) that seem to drive cancer-related ligand expression.

CONCLUSIONS
Following the screening, I plan to validate a few targets through a secondary screen. This magnetic screening method would produce a collection of genes for reversing cancer-associated hypersialyation. I hope to compile the list of genes into an open-source database, catalyzing research in the broader field of tumor glycobiology.

Junior MSc Student Poster Presentations

Engineering Peptide Nanofibres to Optimize the Biointerface for Bacterial Encapsulation

Presenter: Noah Brittain

Noah Brittain[1], Joel Finbloom[1]

[1]*Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, BC, Canada*

BACKGROUND
Most bacteria live in fibrous matrixes called biofilms. Biofilms comprise extracellular biological polymers that provide nanoscale structural support and regulate beneficial bacterial behaviour. We are leveraging this beneficial bacteria-nanofibre interaction to engineer biofilm-inspired self-assembling peptide nanofibres for the encapsulation and oral delivery of therapeutic bacteria. Due to the modular self-assembly process, nanofibre properties can be finely adjusted by changing the sequence of the oligopeptide building blocks. In this study, we aim to investigate how altering the material properties of these nanofibres changes their interaction with bacteria, allowing us to understand better how we can encapsulate therapeutic bacteria in nanostructured systems.

METHODS
Oligopeptides for nanofibre formation were synthesized using solid-phase peptide synthesis and formed into nanofibers using a previously reported pH-induced solubilization method. We then analyzed nanofibre material properties using techniques such as zeta-potential, rheometry, and electron microscopy. The nanofibres were then incubated with the probiotic *Escherichia Coli* Nissle 1917, and bacteria-nanofibre interactions were observed using fluorescence and electron microscopies. Bacterial response was analyzed using optical density measurements and fluorescent metabolic assays. Finally, microscale hydrogels were fabricated from alginate and peptide nanofibres and bacterial encapsulation efficiencies were evaluated.

RESULTS
We showed that oligopeptide sequence altered nanofibre physicochemical properties. In addition, these changes to the nanofibre properties influenced how they interacted with probiotic *E.coli*, displaying no significant effect on bacterial growth but minor effects on bacterial metabolism. Lastly, alginate and nanofibre hydrogels were fabricated and studies are ongoing to evaluate bacterial encapsulation and hydrogel stability.

CONCLUSIONS
We have shown how changes in peptide nanofibre chemistry can alter how these materials interact with the bacteria *E.coli* Nissle 1917. These findings will inform us for future studies on what material properties are best suited to developing a nanofibre-based bacterial encapsulation platform to deliver bacteria to the gastrointestinal tract.

Senior MSc Student Poster Presentations

Implementation of Supervised Machine Learning Models to Predict Drug-Breastmilk Partitioning

Presenter: Akash Panjabi

Akash Panjabi[1], Anil Maharaj[1]

[1]*Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, BC, Canada*

BACKGROUND

Medication safety during breastfeeding is often not well understood, leading to early cessation of breastfeeding or delayed treatment. To assess the safety of medication use during breastfeeding, accurately determining the milk-to-plasma (M/P) ratio is vital. This pharmacokinetic parameter provides an indication of the extent of drug transfer from maternal plasma to breastmilk. Many equations have been developed to predict the M/P ratio, however there is no consensus on which of these works the best for estimating the M/P ratio within a given physicochemical space. Hence, the goal of this work is to select the M/P ratio equation that works the best within a given physicochemical space using machine learning (ML).

METHODS

Several supervised ML models, including Decision Trees, Bootstrap Aggregation, Random Forest, Gradient Boosting, and Support Vector Machines, were used to determine the best method for calculating the M/P ratio. The dataset used consisted of biochemical properties of drugs, maternal characteristics, and pharmacokinetic parameters. Division of the dataset into training and test subsets, and cross-validation, were employed to optimize model parameters. Performance metrics such as Average Fold Error (AFE) and Absolute Average Fold Error (AAFE) were used to evaluate M/P ratio calculation.

RESULTS

Random Forest (RF) classification models appeared to outperform the other algorithms based on preliminary data, demonstrating an AFE of 1.189 and an AAFE of 3.332 when using the most appropriate equation predicted. Feature importance analysis revealed that Log $D_{7.4}$, PSA, pKa, and plasma unbound fraction were significant predictors.

CONCLUSIONS

Random Forest models serve as promising tools for predicting the M/P ratio based on several easily obtainable input parameters. Such models offer a preliminary method of assessing drug safety in lactating women by providing the most appropriate method to calculate the M/P ratio. Further research is required to validate these findings across a broader range of compounds.

Senior MSc Student Poster Presentations

Developing The Minipig for Use in Pharmacokinetic Modeling: Determination of Microsomal and Cytosolic Scaling Factors and Validation of NQO1/NQO2 Metabolism

Presenter: Austin Alphonse Zimmer

Austin Alphonse Zimmer[1], Abby C. Collier[1]

[1]Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, BC, Canada

BACKGROUND
Minipigs are a common pre-clinical animal model, yet they suffer due to poor evaluation of pharmacokinetic parameters. Scaling factors required to estimate compound clearance and elimination from activity such as microsomal/cytosolic protein per gram of organ remain undefined. This is compounded by poor knowledge or minipigs enzyme abundance, expression and activity. Lack of these data hampers minipig usage.

METHODS
Samples (n=4) were harvested from whole organs (liver, kidney and intestine) within 4hr of death and flash frozen. When ready, samples were thawed, wet weight recorded, then homogenized in buffer. Intestinal samples were subjected to enterocyte elution rather than bulk homogenization. Differential centrifugation (10,000xg, 100,000xg) isolated microsomal and cytosolic fractions, enabling scalar quantification based on protein concentration. Microsome quality was by mannose-6-phosphatase assay, and the effect of freeze thaw cycling (n=3) on protein content was determined using BCA and Bradford assays to investigate variation in derived scalar values.

RESULTS
Mean values were: MPPGL/CPPGL: 24.3±3.2, 75.6±17.4; MPPGK/CPPGK : 12.6±4.32, 40.3±6.2, and MPPGI/CPPGI: 1.8±0.71, 9.0±0.77 mg protein/g tissue. Mean liver and kidney microsomal intactness was 74.8±7.6% and 61.3+/-% indicating good integrity. Intestinal intactness was unable to be calculated. Freeze thaw effects were determined for n=3 cycles with all significantly reducing protein levels ($p<0.05$) with each cycle.

CONCLUSIONS
Scaling factors were calculated for the first time in the Yucatan minipig, including demonstrating the negative effects of freeze thawing on microsome and cytosol fractions. Microsomal quality was acceptable after tissue storage at -80C for liver and kidney, but more investigation is required for Intestinal preparations.

Senior MSc Student Poster Presentations

Characterizing the Mechanism of Doxorubicin Mediated SAT1 Induction in Triple-Negative Breast Cancer

Presenter: Caroline Liang

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BACKGROUND
Triple-negative breast cancer (TNBC) is the most aggressive form of breast cancer and the effectiveness of chemotherapy drugs, such as doxorubicin (DOX), is limited by drug resistance. Consequently, there is a need to detect effective drug response early during TNBC chemotherapy. Spermidine/spermine N^1-acetyltransferase (SAT1) is an important catabolic enzyme involved in polyamine metabolism and tumour growth. SAT1 expression is induced following DOX treatment, resulting in increased urine levels of the polyamine pathway metabolite, diacetylspermine. However, the mechanism of DOX mediated SAT1 induction is unknown. DOX downregulates specificity protein 1 (Sp1), which has recently been shown to bind to the SAT1 promoter and act as a transcriptional repressor. Therefore, we hypothesize that DOX induces SAT1 expression and diacetylspermine production via Sp1 degradation.

METHODS
Hs578T TNBC cells were treated in the presence or absence of DOX with: MG132, a proteasome inhibitor that stabilizes all proteins, including Sp1; mithramycin A, an Sp1 inhibitor; or KU-55933, a DNA damage response kinase (ATM) inhibitor. Quantitative PCR (qPCR) was performed to determine whether stabilization or inhibition of Sp1 with or without DOX affects SAT1 mRNA expression.

RESULTS
Hs578T cells treated with DOX demonstrated a significant increase in SAT1 mRNA expression, over twofold compared to controls ($p<0.05$). Interestingly, cells treated with MG132, a combination of MG132 and DOX, and mithramycin A also showed significant increases in SAT1 mRNA expression, with average fold increases of 5.9, 2.2, and 2.6, respectively ($p<0.05$).

CONCLUSIONS
The increase in SAT1 mRNA expression in Hs578T cells following Sp1 inhibition may suggest that the mechanism of SAT1 induction is mediated through Sp1 binding to the SAT1 promoter. Understanding this mechanism will contribute to defining the use of urine diacetylspermine as a non-invasive metabolic biomarker of doxorubicin effectiveness and may be applicable to the usage of other DNA damaging chemotherapy agents.

Senior MSc Student Poster Presentations

The Effect of Changes in Social Ties on Waist Circumference in Aging Adults: Longitudinal Analysis of Canada's Aging Cohort

Presenter: Rana Madani Civi

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BACKGROUND
Social connections are known to influence morbidity and mortality risk, and have been associated with waist circumference, in older adults. However, longitudinal evidence on changes in social ties and waist circumference in Canada, and potential gender differences, is lacking.

METHODS
We analyzed data from the Canadian Longitudinal Study on Aging collected at three time points: baseline, follow-up 1, and follow-up 2. We assessed changes in marital status, living arrangements, and social participation in relation to changes in waist circumference (WC) by gender. Sample sizes varied, with 13,968 participants for marital and living arrangement transitions, and 13,948 for changes in social participation. Mixed models with random coefficients for sampling strata adjusted for age, age-squared, duration, baseline WC, socio-economic indicators, health status, and three provincial variables.

RESULTS
In our sample, consisting of 47% men, divorce was associated with reduced WC in women (-0.53 cm [CI95: -2.02, 0.96]) but increased WC in men (0.80 cm [CI95: -0.66, 2.27]) compared to those who remained partnered. Widowed women had increased WC (0.78 cm [CI95: -0.43, 1.99]), while widowed men showed decreased WC (-0.78 cm [CI95: -2.38, 0.83]), compared to counterparts remaining partnered. Women transitioning to co-living had reduced WC (-0.15 cm [CI95: -1.14, 0.84]), while men had increased WC (0.85 cm [CI95: -0.44, 2.14]) compared to those remaining co-living. Reductions in social participation were linked to significant WC increases in women (0.52 cm [CI95: 0.12, 0.92]); twice the increase in men (0.21 cm [CI95: -0.18, 0.61]). No gender differences were observed for increases in WC from remaining non-partnered or becoming partnered, for becoming lone-living or remaining lone-living, and for increases in social participation, compared to reference groups for both genders.

CONCLUSIONS
Findings indicate that different social tie transitions may be associated with changes in WC among Canadian aging population, and that associations are gendered.

Senior MSc Student Poster Presentations

Novel Therapeutic Targeting of CNOT3 in Acute Myeloid Leukemia

Presenter: Renessa Gomes

Renessa Gomes[1,2], Maryam Ghashghaei[1,2], Brent Page[1], Ly Vu[1,2]

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BACKGROUND

Acute myeloid leukemia (AML) is an aggressive blood cancer characterized by accumulation of immature blood cells. Chemotherapy has remained the standard AML treatment since the 1970s yet 5-year survival rates are <35% in young adults and <15% in adults above 60. The Vu lab uncovered that CNOT3, a subunit of an RNA deadenylation complex, had elevated protein levels in AML cell lines and supported their survival. The goal of my project is to develop a therapeutic approach that depletes CNOT3 protein to preferentially eliminate AML cells.

METHODS

Proteolysis-targeting chimera (PROTAC) are fusion molecules that recruit protein degradation machinery to a specific protein target. We aim to create a PROTAC that induces CNOT3 protein degradation. The most challenging step of PROTAC development is identifying a molecule that binds specifically to the protein target. To find a CNOT3-specific ligand, we are using cellular target engagement by accumulation of mutant (CeTEAM). CeTEAM entails creating tagged CNOT3 mutants which exhibit limited protein stability in cells. The mutant can be used to screen for small molecules whose binding leads to protein stabilization, hence accumulation of the tagged protein in cells.

RESULTS

Computational prediction nominated two mutations S667A and L678Q as unstable CNOT3 mutants. We validated that exogenously expressed CNOT3 S667A and L678Q in MOLM13 cells are less abundant than wild-type (WT) CNOT3, and have insignificant differences in mRNA expression. When protein synthesis is inhibited, WT CNOT3 protein levels remain stable over 16 hours while CNOT3 S667A and L678Q exhibit half-lives of approximately 4 hours. When the proteosome is inhibited, CNOT3 S667A and L678Q demonstrate greater protein accumulation than WT CNOT3.

CONCLUSIONS

CNOT3 S667A and L678Q show evidence of protein destabilization based on degradation rates, protein and mRNA abundance. These results nominate CNOT3 S667A and L789Q as suitable mutants to identify CNOT3 ligands utilizing CeTEAM.

Senior MSc Student Poster Presentations

Lipid Nanoparticles Formulated in the Presence of 300 mM Sodium Citrate Enable Enhanced in vivo Gene Editing with CRISPR/Cas9 Adenine Base Editor mRNA and sgRNA

Presenter: Tyler Thomson

Tyler Thomson[1], Alexandra Birkenshaw[1], Colin Ross[1]

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BACKGROUND

Achieving safe and effective delivery of gene editing systems is a critical step in enabling future therapeutics for the treatment of genetic disorders. As opposed to viral vectors, lipid nanoparticles (LNPs) containing RNA present an especially appealing delivery method, having lower immunogenicity, scalable manufacturing processes, and transient expression of gene editing components that lowers the chances of off-target editing. Work from our collaborators in the lab of Dr. Pieter Cullis recently demonstrated that using 300 mM Na-citrate as the pH 4 loading buffer during LNP synthesis greatly improved functional delivery of mRNA, likely due to improved mRNA stability [1]. We reasoned that incorporating this into the LNP formulation process for gene editor RNA could therefore also improve LNP-mediated gene editing.

METHODS

To assess gene editing, we utilized our luciferase reporter mouse LumA, where successful editing of a defective luciferase transgene results in restoration of luminescent signal, allowing visualization of the efficiency and biodistribution of gene editing. Mice received a single dose of LNPs containing adenine base editor mRNA and sgRNA, formulated using either the standard 25 mM sodium acetate or 300 mM sodium citrate as the pH 4 buffer. Gene editing was assessed using IVIS imaging and terminal tissue luciferase assays.

RESULTS

Live imaging and terminal luciferase assays indicated up to ~10x increases in gene editing in the liver with the 300 mM Na-citrate formulation, relative to LNPs prepared using the 25 mM Na-acetate pH 4 buffer, depending on the ionizable lipid used.

CONCLUSIONS

This work demonstrates that using the 300 mM Na-citrate buffer in LNP formulation enhances the efficiency of RNA-based LNP-mediated gene editing, allowing lower LNP/RNA dosages in future therapeutic applications.

1. Cheng MHY, et al. Induction of Bleb Structures in Lipid Nanoparticle Formulations of mRNA Leads to Improved Transfection Potency. *Advanced Materials* 35, (2023)

PhD Student Poster Presentations

A Discrete Choice Experiment of the Medication Preferences of People with Heart Failure: A Pilot Study

Presenter: Blair MacDonald

Blair MacDonald[1], Logan Trenaman[2], Nick Bansback[1], Mark Harrison[1], Ricky Turgeon[1]

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BACKGROUND
Heart failure affects approximately 750,000 Canadians—impairing their quality of life, lowering their chances of survival, and increasing their risk of hospitalization.[1] Heart failure medications have the potential to substantially improve these outcomes, but at the expense of increased pill burden, risk of side effects, and cost. Knowledge of the values and preferences of people with heart failure is essential for successfully navigating these complex decisions. However, the medication preferences of people with heart failure are currently largely unknown.

METHODS
We conducted a discrete choice-experiment of people with self-reported heart failure using the online Prolific platform. Participants were presented with a choice between taking one of two different drug regimens or opting out of the decision (i.e., taking no additional medications). These choices were described according to their impact on quality of life, survival, hospitalization, side-effects, cost, and pill burden. The results were analyzed using conditional logistic regression.

RESULTS
Of the 101 participants, the mean age was 55 years old, 62% were male, and 26% reported no college or university education. The majority of participants (89%) agreed or strongly agreed that the questions were easy to understand. The most important treatment attributes were cost, quality of life, and survival. The least important attributes were the risk of side effects and pill burden.

CONCLUSIONS
This pilot study of a discrete choice experiment indicates that the primary trade-off for patients with heart failure may be between improving survival probability/quality of life and increased cost.

1. Falling Short: How Canada is failing people with heart failure – and how we can change that. (2022).

PhD Student Poster Presentations

Design of Neutrophil-inspired Antimicrobial Polyelectrolyte Nanocomplexes

Presenter: Chinekwu Nwagwu

Chinekwu Nwagwu[1], Sara Jamshid-Nezhad[1], Joel A. Finbloom[1]

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BACKGROUND
Neutrophils provide defense against invading pathogens by releasing dense webs of DNA and histones to engulf bacteria in neutrophil extracellular traps (NETs) while releasing antimicrobials to initiate the eradication of bacteria. The goal of this work was to create nanoparticles with antibacterial, bacterial-entrapment, and pH-responsive swelling properties that mimic NETosis. The nanocomplexes were formed through electrostatic attraction between positive and negative polymers and loaded with an antibiotic, tobramycin. The aim of this study was to develop pH responsive NCs that expand to entrap bacteria and then release the loaded antimicrobial agent. We hypothesize that this bioinspired and stimulus-responsive method of administering antibiotics will reduce antibiotic adverse effects and increase therapeutic efficacy.

METHODS
The nanocomplexes (NCs) were formulated by combining the drug, tobramycin, with poly cationic polymers (Trimethyl chitosan and Poly ethylene imine) and polyanionic polymers (Polymethyl vinyl ether-alt-maleic acid) in varying ratios. The effect of buffer compositions, pH and incubation time on the nanocomplexes were evaluated. In addition, other physicochemical parameters of the NCs such as size, PDI, surface charge and encapsulation efficiency were also evaluated.

RESULTS
Tobramycin-loaded nanocomplexes with particle size of about 250 nm and low PDI (< 0.1) were produced. The nanocomplexes also showed remarkable drug loading (>80 %), with pH responsive swelling from approximately 250 nm to > 3 um. The nature as well as proportions of the polymers used played a crucial role in determining the characteristics of the NCs. The buffer type, duration of incubation and pH also affected the properties of the NCs.

CONCLUSIONS
The study showed that the nanocomplexes possess promising features that could be explored in the design of more effective delivery systems for antimicrobial agents. However, further assessments such as microscopic examinations to understand particle swelling behavior are required to optimize these nanocomplexes.

PhD Student Poster Presentations

Alcohol and Aldehyde Metabolism Gene Expression in the Minipig Liver

Presenter: Maria Beletsky

Maria J. Beletsky[1], Austin A. Zimmer[1], Dickson Lai[1], Alexander D. Smith[1], Michael J. Doerksen[1], Rei Sato[1,2], Miki Nakajima[2], Abby C. Collier[1]

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BACKGROUND
Improved understanding of alcohol and aldehyde metabolism is critical in the context of drug development because drugs or drug metabolism products (including intermediates) are likely to include alcohol and or aldehyde moieties. For approximately two decades, minipigs have been a popular pre-clinical model due to their high homology to humans for the purposes of research in pharmacology and toxicology. However, expression of alcohol dehydrogenase (ADH), aldehyde dehydrogenase (ALDH), and aldehyde oxidase (AO) is not characterized in this species despite the importance of these enzymes in alcohol and aldehyde metabolism. This study aims to characterize ADH, ALDH, and AO expression in the minipig liver to elucidate metabolism through these hepatic pathways.

METHODS
ADH, ALDH, and AO gene expression was investigated in female minipig liver tissue. RT-PCR analysis was conducted to confirm the presence or absence of gene expression for 28 genes corresponding to different ADH, ALDH, and AO enzymes in the liver samples.

RESULTS
ADH, ALDH, and AO gene expression was characterized and appeared to vary between individual minipigs.

CONCLUSIONS
Careful choice of species, sex, and strain of pre-clinical model is imperative when choosing a pre-clinical model for study of drug metabolism and clearance. This study aims to elucidate alcohol and aldehyde metabolism in the minipig liver for better informed and improved use of minipig models in human endo- and xenobiotic metabolism research.

PhD Student Poster Presentations

DYRK1b: A Novel Regulator of Extracellular Vesicle Dynamics in Breast Cancer

Presenter: Sina Halvaei

Sina Halvaei[1], Nikki Salmond[1], Karla Williams[1]

[1]*Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, BC, Canada*

BACKGROUND

Extracellular vesicles (EVs), including exosomes and ectosomes, play pivotal roles in intercellular communication by shuttling biologically active molecules between cells. In breast cancer, EVs facilitate tumor progression, metastasis, and therapy resistance. In this study, we employed nanoscale flow cytometry to investigate EV dynamics and screen kinase inhibitors affecting EV release from MDA-MB-231 breast cancer cells.

METHODS

We transfected MDA-MB-231 with ZsGreen plasmid, and validated nanoscale flow cytometry for detecting green EVs, ensuring specificity and characterizing EV populations. Through nano-particle tracking analysis, electron microscopy, western blotting for EV markers, differential ultracentrifugation and size-exclusion chromatography, we confirmed the presence and size distribution of EVs, highlighting distinct marker expression patterns between small and large EVs. Subsequently, we performed a high-throughput screen with 156 kinase inhibitors, identifying AZ191 as a potent inhibitor of EV release. Then we validated this kinase inhibitor with siRNA knockdown of its target protein, DYRK1b and further validated our result with differential ultracentrifugation, size-exclusion chromatography and immunohistochemistry.

RESULTS

Validation experiments demonstrated that AZ191 significantly reduced EV release, particularly small EVs, without affecting cell viability or proliferation. Further, siRNA-mediated knockdown of DYRK1b, the target of AZ191, corroborated its role in regulating EV release. Remarkably, DYRK1b silencing altered the intracellular distribution of the EV marker CD63, suggesting a role for DYRK1b in EV trafficking.

CONCLUSIONS

In conclusion, our study establishes a robust platform for high-throughput analysis of EV dynamics via flow cytometry and underscore DYRK1b as a novel regulator of EV biogenesis and release in breast cancer cells.

PhD Student Poster Presentations

Phthalate Exposure and Placental Cell Lines; a Literature Review Comparing First and Term Like Placental Cell Lines with Exposure to DEHP and its Metabolites

Presenter: Stuart Knight

Stuart J. Knight[1], Michael W.H. Coughtrie[1], Abby C. Colliler[1]

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BACKGROUND

Phthalates are common in everyday objects including cosmetics, food packaging and medications. They are endocrine-disrupting chemicals affecting hormone signaling, hence constant exposure to phthalates could pose problems in pregnancy, specifically at the level of the placenta—an organ at the fetal-maternal interface. Moreover, detection of phthalates is challenging since differentiation between background and environmental exposures is difficult.

METHODS

A literature search was conducted on Medline and PubMed to investigate the effects of the major phthalate Di-2-ethylhexyl phthalate (DEHP) and its major metabolite mono-2-ethylhexyl phthalate (MEHP) on the placental cell lines HTR-8/SVneo and BeWo. An additional search was performed to locate literature for analysis of DEHP and its metabolites, thereby guiding the development of our LC/MS method to detect phthalate exposure.

RESULTS

After inclusion/exclusion criteria were satisfied, eight papers were evaluated. Amongst HTR-8/SVneo papers, there was a preference for MEHP (five papers) being detected analytically vs. DEHP (two papers), with no other metabolites measured. Studies reported data on DEHP in urine/blood with detection ranging from 0.1-500ng/ml. In developing our analytical method over this range, overloading was observed around 100ng/ml and above, possibly due to the increased sensitivity of modern instruments.

CONCLUSIONS

Almost no cell line studies directly relate to the analytical detection of phthalates, likely demonstrating difficulty separating environmental exposure from background levels. Other topics including reactive oxygen species and trophoblast biology were discussed, but none addressed placental hormone expression; a knowledge gap with respect to phthalate exposure and hormonal balance in pregnancy. DEHP and metabolite measurement is highly sensitive and separating exposure from background contamination is challenging, as shown in our preliminary results. This project has promise for understanding phthalate exposure in pregnancy and mechanistic implications (using placental cell lines) of phthalate exposures, including effects on reproductive hormones.

PhD Student Poster Presentations

Rational Design of a Novel Adenosine Base Editor for Clinical Applications

Presenter: Tessa Morin

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BACKGROUND
Gene editing is a potential curative treatment for genetic diseases. However, current gene editing technologies are limited in their use and safety. New gene editors have been developed to address this problem, such as CRISPR/Cas9-derived base editors, which enzymatically convert a target base to another. However, base editors are also capable of creating unwanted mutations, known as off-target edits, which can potentially lead to tumourgenesis or additional mutations at the target site. Attempts have been made to improve the existing adenine base editors, but are limited in their efficacy and/or safety.

In our study, we investigated whether novel combinations of existing mutations, or de novo mutations in the deaminase of the standard base editor ABE8e could reduce unwanted bystander edits while maintaining or exceeding on-target editing. We hypothesize that our novel TadA deaminase will have better on-target versus off-target editing compared to ABE8e.

METHODS
We successfully developed a novel cloning strategy to screen different deaminases and different protein linkers for our base editor. We then cloned new base editors with either novel combinations of existing mutations, *de novo* mutations, or differing protein linkers to the Cas9 protein. The base editors were screened on multiple different sites in HEK293 cells to determine the editing window, efficacy, and number of bystander mutations compared to ABE8e. Genomic DNA was extracted, PCR-amplified, and sequenced to analyze the level of editing.

RESULTS
Two mutations (V82S and Q154R) have shown promising results for widening the editing window of TadA8e, while combinations of N108K, N108Q, L145T, A48M, and P29A have reduced the editing window.

CONCLUSIONS
Our data show there are safer and effective base editors compared to current standard. With further optimization, these base editors could be a better choice for therapeutic gene editing.

Postdoctoral Fellow Poster Presentations

Chemokine Receptor CCR7 Regulates Invadopodia Formation in Triple Negative Breast Cancer

Presenter: Merlyn Emmanuel

Sumreen Javed[1*], Merlyn Emmanuel[1*], Vivi Chen[1], Nazarine Fernandes[1] and Karla Williams[1]

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**These authors have contributed equally to the work*

BACKGROUND

Cellular migration and invasion through a tissue barrier is an important process observed in both physiological and pathological conditions. Navigating endothelial cell barriers and remodeling the extracellular matrix (ECM) are key processes in successful cell invasion. Cancer cells employ protrusive structures called invadopodia to navigate a vascular endothelial barrier and degrade the ECM. We have discovered that CCR7, a chemokine receptor, is present at invadopodia and responsive to chemokine CCL19. In context of breast cancer, CCR7 is linked to tumor aggressiveness and metastasis.

METHODS

Using classical cell-based assays (ECM invasion and TEER) to measure the invasion of cancer cells across the lymphatic junctions formed by HDLEC (human dermal lymphatic endothelial cells) we investigated the role of CCR7 in invadopodium formation and chemosensing. The mouse model was used to determine the contribution of lymphatic metastases to lung tumor burden.

RESULTS

Lymph node (LN) metastases from breast cancer patients had higher expression levels of key invadopodial protein -Tks5, relative to the matched primary tumor. A lymph node homing breast cancer cell line (231LN) had significantly higher levels of Tks5 and CCR7 expression relative to its parental cell line (231). Tks5KO impaired tumor cell invasion across a lymphatic endothelium. CCL19 increased 231LN lymphatic invasion and this response was blocked in Tks5KO cells. CCL19 increased invadopodia formation through phosphorylation of CCR7 demonstrating a functional role for CCR7 at invadopodia. LN removal in mice lead to a significant reduction in metastatic lung tumor burden highlighting the importance of LN as intermediary site for metastasis.

CONCLUSIONS

In normal physiology, CCR7 is important in regulating directed migration of mature dendritic cells. Our data shows that CCR7 at invadopodia is important for chemosensing and persistent degradation *via* these structures. Therefore, CCR7 along with TKS5 may hold prognostic, or therapeutic, value for disease diagnosis and to predict patient outcomes.

Postdoctoral Fellow Poster Presentations

An Innovative Injectable Thermosensitive Hydrogel for Biomedical Applications

Presenter: Tejinder Kaur

Tejinder Kaur[1], Shyh-Dar Li[1]

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BACKGROUND
Surgically implanting hydrogels is an inconvenient and painful method for patients. On the other hand, injectable thermosensitive hydrogels are liquid at low temperature which can be easily injected using conventional syringes and exhibit sol-gel phase transition inside the body. The free flowing nature of these hydrogels at room temperature makes them suitable for encapsulating drugs, cells or other bioactive agents by simple mixing. In the present work, a hyaluronic acid based biodegradable and injectable thermosensitive hydrogel was developed and then studied for its biomedical applications.

METHODS
Briefly, an optimized concentration of hyaluronic acid was mixed with varying concentrations of a cross-linking agent to develop a hydrogel solution and the pH was adjusted to ~7.4. Thus developed hydrogel formulations were tested for sol-gel phase transition at 37°C and gelation time. The hydrogels were characterized for their physicochemical properties, such as molecular interactions, swelling and degradation rate. Different drugs were dissolved in hydrogel solutions at 4°C and the temperature was raised to 37°C to examine *in-vitro* release profiles. Additionally, different hydrogels were applied on various cell culture models, and their effects on cell viability, cell proliferation, cell encapsulation, cell migration, and wound healing were evaluated.

RESULTS
The concentration of the cross-linking agent influenced the gelation time of the hydrogels. Sustained drug release was observed for various drugs, including FITC-BSA and ovalbumin. The cellular compatibility of the innovative hydrogel was better than the commercially available thermosensitive hydrogels, such as poloxamer and chitosan-glycerol phosphate. The cells were proliferating even when encapsulated in the innovative hydrogel matrix. In the presence of the innovative hydrogel, fibroblast migration was the fastest compared to other previous reported hydrogel systems, inducing superior wound healing activity in human skin equivalents.

CONCLUSIONS
In conclusion, an innovative, injectable thermosensitive hyaluronic acid-based hydrogel with great potential for biomedical applications was developed.