Conference 2018:

Translating Innovative Technology to Patient Care

May 22 - 25, 2018
Chelsea Hotel, Toronto, ON, Canada

A joint conference of:

Canadian Society for Pharmaceutical Sciences
Canadian Society of Pharmacology and Therapeutics
Canadian Chapter of Controlled Release Society

Conference Co-Chairs:

Catherine Lau, Janssen Inc., Toronto, ON
Micheline Piquette-Miller, University of Toronto, Toronto, ON

Conference Organizing Committee:

From CSPS:
Frank Abbott, University of British Columbia, Vancouver, BC, Christine Allen, University of Toronto, Fakhreddin Jamali (University of Alberta)
From CSPT: Kerry Goralski (Dalhousie University), Randee Holmes (CSPT), Brad Urquhart (University of Western Ontario)
From CC-CRS: Marc Gauthier (INRS)

Canadian Society for Pharmaceutical Sciences

Welcome to Toronto and to the celebration of the **21st** Anniversary of CSPS!

We are pleased to once again collaborate with the Canadian Chapter of the Controlled Release Society and also the Canadian Society of Pharmacology and Therapeutics to bring you an exciting program - *From Innovation to Patient Solution.* We hope you find the conference sessions to be valuable and thought-provoking.

The Canadian Society for Pharmaceutical Sciences (CSPS) is a non-profit organization established in 1997 to foster excellence in pharmaceutical research. Our members are scientists and educators involved in all aspects of pharmaceutical sciences including academia, industry and government. A major objective is to build partnerships and develop a strong voice to encourage government, academia, and industry to advance pharmaceutical R&D innovation in Canada.

The electronic *Journal of Pharmacy and Pharmaceutical Sciences* is the official, international journal of CSPS and can be accessed on our website.

Enjoy the program while meeting old friends and making new ones!

Catherine Lau, Ph.D.
President, CSPS (2018-2019)

CSPS Board of Directors includes representatives from industry and academia and government.
The 2018 Board is: **Catherine Lau,** President (2018-2019) (Janssen Inc.), **Christine Allen,** President-Elect & Treasurer (University of Toronto), **Frank Abbott**, Past President (University of British Columbia), **Noriko Daneshtalab**, Secretary (Memorial University of Newfoundland), **Directors: Jane Alcorn** (University of Saskatchewan), **Denis deBlois** (Université de Montréal), **Ron Boch** (BIOTECanada), **Arshia Ghani** (Pfizer), **Emmanuel Ho** (University of Waterloo), **Fakhreddin Jamali** (University of Alberta), **Agnes Klein** (Health Canada), **Elisabeth Kovacs (**Apotex), **Ted Lakowski** (University of Manitoba), **Co Pham** (Health Canada), **Franklyn de Silva**, Trainee Rep **(**University of Saskatchewan)

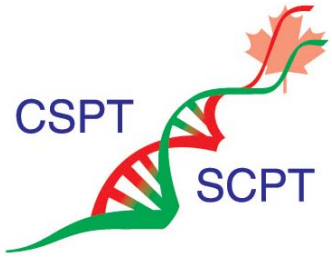
CSPS 2018 Awards - Congratulations to the following:

CSPS Lifetime Achievement Award: Gordon Amidon, University of Michigan
CSPS Fellow: Raimar Loebenberg, University of Alberta; Krishnan Tirunellai, Health Canada
Gattefossé Canada/CSPS Lipid-Based Drug Delivery Award: Shannon Callender, University of Waterloo
GSK/CSPS National Undergraduate Student Research Program Awards:
Jonathon Thomson (University of Alberta)**, Anne Nguyen** (University of British Columbia), **Kelsey Mann** (Dalhousie University), **Rachel Ward** (Memorial University of Newfoundland), **Francis Lefebvre** (Université de Montréal), **Grace Cuddihy** (University of Saskatchewan), **Wendy Siu** (University of Toronto), **Stephanie De Jong** (University of Waterloo)

Poster Awards (Winners to be announced Friday afternoon):

- Antoine A. Noujaim Award of Excellence, sponsored by the Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta
- Servier Canada Poster Awards
- Cedarlane Award of Excellence
- CSPS Best Poster Awards

Special thanks for the support of our Sustaining Partner: Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta.



Canadian Society of Pharmacology and Therapeutics

On behalf of the Canadian Society of Pharmacology and Therapeutics (CSPT), it is our pleasure to welcome you to our Annual Meeting in Toronto. This year, we are joining forces with our partners of the Canadian Society of Pharmaceutical Sciences (CSPS) and the Canadian Chapter of Controlled Release Society (CC-CRS) to bring together a critical mass of academic researchers, clinicians and industry professionals in offering an outstanding conference program and research forum.

CSPT is the voice of Canadian pharmacology. We are a national not-for-profit organization created with the goal of fostering the application of educational and research excellence to drug discovery and therapeutic choices. Our membership is diverse blend of clinicians, academic investigators, industrial partners and trainees interested in the goal of more effective and safer drug therapy. CSPT is the official Canadian member of the International Union of Basic and Clinical Pharmacology (IUPHAR) and as such is an international voice for Canadian science and innovation in drug discovery and therapeutic excellence.

This year's meeting promises to be exceptional with a great slate of speakers and a host of interesting oral and poster presentations. In addition to offering scientific excellence, the meeting will be held in the heart of Toronto, one of the most vibrant and exciting cities in the world.

Thank you for your attendance and we look forward to serving you and interacting with you in the coming months! If you'd like to get involved in CSPT, we are always looking for new and motivated individuals to be involved – please contact us! Visit our website at https://pharmacologycanada.org for information on our society and to learn about updates on our activities throughout the year.

Congratulations to the 2017 CSPT award winners:

Distinguished Service and Education Award: George Dresser, Western University
Senior Investigator Award: Anne-Noël Samaha, Université de Montréal
Clinical Fellowship Award: Gavin Sun, Western University
Postdoctoral Award: Galen Wright, University of British Columbia
Publication Award: Jean-François Trempe, McGill University

CSPT Executive Committee

President: Michael Rieder (Western)
Vice President: Kerry Goralski (Dalhousie)
Secretary: Marc Gauthier (INRS)
Treasurer: John McGuire (Memorial)
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Scientific Program Chair: Bradley Urquhart (Western)
Education Committee Chair: Cindy Woodland (Toronto)
Outreach Committee Chair: Bruce Carleton (UBC)
Royal College Liaison: Doreen Matsui (Western)

Canadian Chapter of Controlled Release Society

On behalf of the Canadian Chapter of the Controlled Release Society (CC-CRS), it is my pleasure to welcome you to our Annual Chapter Symposia in Toronto. This year, we once again join forces with our colleagues at CSPS and CSPT to bring together a critical mass of academics and industry professionals to offer an outstanding conference program. The topic of this meeting "Translating Innovative Technology to Patient Care" is a fundamental motivation of our Society, and one that we hope to achieve through the research we showcase at this Meeting.

CC-CRS represents over 250 Canadian academics and industry professionals across scientific, engineering, and medical fields. We are involved in the science and technology of controlled delivery of drugs and therapeutic agents in human and animal health, and of other active agents in environmental, consumer, and industrial applications. We encourage you to join our Society (membership is free!) and to participate in the networking opportunities we organize across Canada. In particular, we would welcome you to attend our regional events that bring together local students, professionals, and industry leaders in the area of controlled release – in the past, we have held events in Winnipeg, Toronto, and Montreal and plan to broaden these events in the coming year across Canada. This year, for the second time in our history, we are also please to invite you to our pre-conference workshop entitled 'Formulation and Delivery of Biologics: Vaccines, Peptide/Protein, and Gene Therapeutics', which provides an opportunity to learn for academic and industry leaders on this important topic. Finally, we encourage you to attend the Annual Meeting & Exposition of our parent body, the international Controlled Release Society (CRS), taking place in New York City, July 22–24, 2018 – an ideal spot to access the latest in delivery science worldwide!

Thank you for your attendance and we look forward to serving you and interacting with you in the coming months! If you'd like to get involved in CC-CRS, we are always looking for new and motivated individuals to be involved – please contact us! Visit our website at http://cc-crs.com for updates on all our activities throughout the year.

CC-CRS Board of Directors
President: Marc A Gauthier (INRS)
Secretary: Marta Cerruti (McGill)
Treasurer: Larry Unsworth (Alberta)
Past President: Emmanuel Ho (Waterloo)
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Student Board Members: Soudeh Tehrani (UdeM)

Sincerely,

Marc A. Gauthier

CSPS / CSPT / CC-CRS 2018 Conference Program

TUESDAY, MAY 22, 2018	
1:00 - 5:00 PM	**Industry Day: *Innovation and Management of Modern Pharmaceuticals*** *(Chairs: Andrew Casey, BIOTECanada, and Christine Allen, University of Toronto)* Room: Churchill Ballroom
1:00 PM	**Opening and Welcome:** Catherine Lau, CSPS President & Conference Co-Chair
	Introductory Remarks: Andrew Casey, BIOTECanada
1:10 - 2:00 PM	**PLENARY: Mary Haak-Frendscho**, Blueline Bioscience & Versant Ventures *The View From Here: Innovation Canadian Style*
2:00 - 2:15 PM	**MaRS Innovation**: **Raphael (Rafi) Hofstein**, President & CEO *MaRS Innovation: Modern Approaches to Bridging the Valley of Death*
2:15 - 2:30 PM	**JLABS**: **Allan Miranda**, Head of JLABS @ Canada *JLABS @ Canada Catalyzing Innovation*
2:30 - 2:45 PM	**Avicanna**: **Aras Azadian**, President & CEO *Avicanna and Evidenced Backed Delivery of Medical Cannabinoids*
2:45 - 3:00 PM	**Cyclica Inc**.: **Stephen MacKinnon**, Director of Research and Development, Cyclica Inc. *Structure-Based and AI-Augmented Proteome Screening for Drug Discovery*
3:00 - 3:15 PM	***Coffee & Tea Break***
3:15 - 3:30 PM	**Pendant Biosciences**: **Shawn Glinter**, CEO *From the Bench to the Board Room: The Things Nobody Tells You!*
3:30 - 3:45 PM	**Panag Pharma**, Halifax: **Melanie Kelly**, Chief Scientific Officer, and **Tetra Bio Pharma**, Montreal: **Guy Chamberland**, Chief Scientific Officer *Navigating the Cannabis Pharma Space*
3:45 - 4:00 PM	**Mirexus Inc.**: **John Dutcher**, Founder *Phytoglycogen Nanoparticles in Nanomedicine: Novel Drug Delivery, Anti-Infective & Immunomodulatory Agents*
4:00 - 4:15 PM	**Encycle Therapeutics**: **Jeffrey Coull**, CEO *Nacellins: New Therapeutic Entities for Challenging Targets*
4:15 - 4:30 PM	**ImmunoBiochem Inc.: Anton Neschadim**, CEO *Targeting the Cancer Cell Secretome to Overcome Tumor Heterogeneity*
4:30 - 4:45 PM	**IMV Inc.: Genevieve Weir,** Director of Research *Improving Immune Responses to Cancer Antigens Using a Nanoparticle Formulation that Targets Lymph Node Cells*
4:45 PM	***Session Summary*** *Christine Allen, University of Toronto*
5:30 - 7:00 PM	***Welcome Reception: CSPS, CSPT, CC-CRS*** *Churchill Court*

WEDNESDAY, MAY 23 - MORNING SESSIONS

7:00 AM	***Registration & Poster Set-Up***		
7:00 - 9:00 AM	**Trainee Breakfast & Session: Nana Lee**, Faculty of Medicine, University of Toronto *Creating Your Career Path with your Grad Degree* Trainee Breakfast 7:00 - 7:30 AM, Session 7:30 - 9:00 AM Room: Rosetti		
8:30 AM	***Coffee & Muffins***		
9:00 - 9:05 AM	**Welcome from:** - CSPS - Cathy Lau, President - CSPT - Kerry Goralski, Vice President - CC-CRS - Marc Gauthier, President		
9:00-10:00 AM	**PLENARY SESSION: David Juurlink**, Sunnybrook Health Sciences Centre *The North American Opioid Crisis from 30,000 Feet* *Chair: Tuan Trang, University of Calgary* Room: Churchill Ballroom		
10-10:30 AM	***Coffee & Tea Break: Posters, Exhibitors, & Networking***		
10:30 AM - 12:30 PM	**SESSION 1A: OPIOID CRISIS** *Chair: David Juurlink, Sunnybrook Health Sciences Centre* Room: Churchill Ballroom	**SESSION 1B: REGULATORY REFORMS** *Chair: Cathy Parker, Director General, BGTD, Health Canada* Room: Rosetti	**SESSION 1C: CROSSING BIOLOGICAL MEMBRANES** *Co-Chairs: Emmanuel Ho, Univ. of Waterloo, and Kerry Goralski, Dalhousie University* Room: Wren
10:30	*Opioid Use and Adverse Events: Emerging Trends and Policy Impacts* **Tara Gomes**, Li Ka Shing Knowledge Institute of St. Michael's	*Improving Access to Innovative Medicines: Health Canada's Regulatory Reform Initiative* **Catherine Parker**, Health Canada	*Improving Predictions of Renal Anionic Drug Transport* **Ryan Pelis**, Dalhousie University
11:00	*Pharmacological Strategies for Harm Reduction in Opioid Use Disorder: An Overview* **Jessica Leen**, University of Toronto	*CADTH in 2018: Crossroads, Inflection Points, and Partnerships* **Heather Logan**, Canadian Agency for Drugs & Technologies in Health (CADTH)	*Disruption of Model Membranes by Surfactants used in Gene Delivery* **Shawn Wettig**, University of Waterloo
11:30	*Nudges, Pushes, Policy and St Francis: Perspectives on the Opioid Crisis* **Shawn Bugden**, Memorial University of Newfoundland	*PMPRB Framework Modernization* **Doug Clark**, Patented Medicine Prices Review Board, Govt. of Canada	*Medicating the Brain: The Challenges of Getting Drugs Past the Blood-Brain Barrier* **Donald Miller**, University of Manitoba
12:00	*HPFB Activities in Support of the Federal Action on Opioids* **Emma Spreekmeester**, Health Canada	***Panel Discussion***: Speakers plus: **Ed Dybka**, QIV Capital (Past President, AstraZeneca Canada Inc.) **Durhane Wong-Rieger**, Consumer Advocare Network	*Optimizing Nanoparticle Interactions with Macrophages and Endothelial Cells for Improved Site-Specific Delivery* **Joy Wolfram**, Mayo Clinic
12:30 - 1:00	**CSPS Lifetime Achievement Award: Presentation & Lecture**: **Gordon Amidon,** University of Michigan *Don't Throw the BA/BE out with the Bathwater: (Mechanistic Oral BE)* *Chair: Fakhreddin Jamali, University of Alberta* Room: Rosetti	**CSPT Distinguished Service and Education Award**: **George Dresser**, Western University *Translating Health Technology at the most Challenging Interface: The Physician/Patient Interaction* Room: Wren	
1:00 - 1:30	***Lunch break (on your own)*** ***Posters, Exhibitors, and Networking***		

WEDNESDAY, MAY 23 - AFTERNOON SESSIONS			
1:30 - 2:30	***Poster Session, Exhibitors***		
2:30 - 5:10	**SESSION 2A: KNOWLEDGE TRANSLATION – FROM REAL WORLD EVIDENCE TO CANADIAN HEALTH CARE NEEDS** *Chair: George Wells, University of Ottawa, and University of Ottawa Heart Institute* Room: Churchill Ballroom	**SESSION 2B: PHARMACEUTICAL POTENTIAL OF STEM CELL & CRISPR-MEDIATED GENE MODIFICATIONS** *Chair: Jeffrey Henderson, University of Toronto* Room: Rosetti	**SESSION 2C: CSPT TRAINEE ORAL PRESENTATIONS** *Chair: Tuan Trang, University of Calgary* Room: Wren
2:30	*Public Payer Perceptions of the Value of Real World Evidence* **Don Husereau**, University of Ottawa, School of Epidemiology and Public Health	*Stem Cell Activation to Promote Self-repair of the Injured Nervous System* **Cindi Morshead**, Donnelly Centre for Cellular and Biomolecular Research	**Galen Wright**, University of British Columbia **Khaled Adb-Elrahman**, Ottawa University **Britt Drögemöller**, University of British Columbia **Anish Engineer**, Western University **Elizabeth Greco**, Western University **Shrinidh Joshi**, North Dakota State University
3:00	*Improving the Use of Real World Evidence in the Regulatory Environment: Where are we Heading?* **Rhonda Kropp,** Marketed Health Products Directorate, Health Canada	*A Stemness-based Drug Screen to Target Acute Myeloid Leukemia Stem Cells* **Jean Wang**, Princess Margaret Cancer Centre, Univ. Health Network	
3:30	***Coffee & Tea Break: Posters, Exhibitors, & Networking***		
4:00	*Canadian Network for Observational Drug Effect Studies: Using Real-World Evidence to Inform Regulatory Decisions* **Robert Platt**, CNODES and DSEN	*Opening the Gate for Pluripotent Stem Cell-based Therapies* **Andras Nagy**, Lunenfeld-Tanenbaum Research Institute, Sinai Health System	**Anette Surmanski,** Western University **Markus Gulilat,** Western University **Eliza McColl,** University of Toronto **Kamelia Mirdamadi,** University of Toronto **Tessa Bendyshe-Walton,** University of British Columbia **Jay Fang,** Western University **Pierre Thibeault,** Western University **Yong Jin (James) Lin,** Western University
4:30	*Life-Cycle HTA: Unlocking the Potential for Real World Evidence* **Tammy Clifford**, CADTH	*Network Analysis of Cell Death Signaling Pathways via CRISPR-mediated Modification in Embryonic Stem Cells and Derivatives* **Jeffrey Henderson**, University of Toronto	
5:00 - 5:10 PM		**Selected CSPS trainee abstract presentation:** *Investigating the Role of the IKKβ Protein Kinase in Vascular Remodeling Events* **Francis Lefebvre**, Université de Montréal	
5:15 - 6:15 PM		**Launch of CSPS Young Scientist Network** We are building a community known as the *CSPS Young Scientist Network* to bring together trainees pursuing pharmaceutical sciences across the country. This meeting will be an opportunity for anyone who is interested in joining to offer feedback about how they would like the network to operate and to establish points of contact at the various schools across the country.	
7:00 PM	[Free Evening] - **Toronto Blue Jays Game**		

THURSDAY, MAY 24 - MORNING SESSIONS

7:00 AM	***Registration & Poster Set-Up***		
8:00 AM	***Coffee & Muffins***		
8:30 - 9:30 AM	**PLENARY SESSION: Tak Mak**, Ontario Cancer Institute, Princess Margaret Hospital, Toronto *The Fourth Pillar of Cancer Treatment: It Takes a Village* *Chair: Catherine Lau, Janssen Inc.* Room: Churchill Ballroom		
9:30 - 10:00 AM	***Coffee & Tea Break: Posters, Exhibitors, & Networking***		
10:00 AM - 12:00 PM	**SESSION 3A: IMMUNO-ONCOLOGY** *Chair: Pamela Ohashi, Princess Margaret Cancer Centre* Room: Churchill Ballroom SPONSORED BY: CDRD	**SESSION 3B: THE GUT MICROBIOME AS A NOVEL THERAPEUTIC TARGET** *Chair: Brad Urquhart, Western University* Room: Rosetti	**SESSION 3C: PRACTICAL PHARMACOLOGY: CASE STUDIES FROM ACROSS THE COUNTRY** *Chair: George Dresser, Western University* Room: Wren
10:00	*10:00 - 10:20* *CAR Therapy: The CD19 Paradigm and Beyond* **Michel Sadelain**, Memorial Sloan-Kettering Cancer Center, NYC	*Overview of the Microbiome and its Potential Role in Therapeutics* **Michael Surette**, McMaster University	*10:00: Clearing Up Controversies Around Carfentanil* **Jessica Leen**, University of Toronto *10:15: A Case of Unilateral Adrenal Adenoma with Resistant Hypertension* **Marc Chretien**, Western University
10:30	*10:20 - 10:40* *A Trans-Canada Highway for CAR-T Cells* **Brad Nelson**, BC Cancer Agency - Deeley Research Centre	*Microbial Effects on Innate and Adaptive Immunity* **Kathy McCoy**, University of Calgary	*10:30: Improving Outcomes for Childhood Cancer Patients Using Genomics-guided Treatment Optimization* **Catrina Loucks**, University of British Columbia
11:00	*10:40 - 11:00 -* *A New Generation CAR Containing a JAK–STAT Signaling Domain Mediates Superior Antitumor Effects* **Naoto Hirano**, Princess Margaret Cancer Centre, UHN	*Fecal Microbial Transplants: Treatment of C. Difficile and Beyond* **Michael Silverman**, Western University	*10:45: Choosing the Right Antihypertensives for your Pregnant Patient* **Albayada Medhar**, Western University
11:30	*11:00 - 11:20* *Immuno-Oncology Combinations in Clinical Development* **Lillian Siu**, Princess Margaret Cancer Ctr *11:20* Panel Discussion with: Session Speakers + **Jian Wang**, Health Canada **Ismael Samudio**, CDRD	*Unexplained Atherosclerosis and Metabolic Products of the Intestinal Microbiome* **David Spence**, Western University	*11:00: Genetic Screening and Cannabis Induced-Psychosis: Who, What and When?* **Gavin Sun**, Western University *11:15:* **CSPT Clinical Fellowship Award Lecture:** **Gavin Sun**, Western University
12:00 - 12:30			*11:45:* **CSPT Post-Doctoral Award Lecture:** **Galen Wright**, University of British Columbia Room: Wren
12:30-1:30	***Annual General Meetings: CSPS** (Churchill), **CSPT** (Wren), **CC-CRS** (Rosetti)* ***Lunch break (on your own) following AGMs*** ***Posters, Exhibitors, and Networking***		

THURSDAY, MAY 24 - AFTERNOON SESSIONS

1:30 - 2:30	***Poster Session***		
2:30 - 5:10	**SESSION 4A: TRANSLATIONAL MEDICINE** *Co-Chairs: Ming Tsao, Ontario Cancer Institute; Janet Dancey, Canadian Cancer Trials Group & Queens University* Room: Churchill Ballroom	**SESSION 4B: CANNABINOIDS** *Chair: Rachel Tyndale, CAMH* Room: Rosetti	**SESSION 4C: INNOVATIVE BIOMATERIALS FOR DRUG DELIVERY** *Co-Chairs: Todd Hoare, McMaster University, Marta Cerruti, McGill University* Room: Wren
2:30	*2:30-2:50* *Opening Pandora's Genome: Rethinking Molecular Diagnostics* **Aly Karsan**, BC Cancer Agency	*Therapeutic Potential of CB1 Allosteric Modulators* **Ruth Ross**, University of Toronto	*Trigger-Amplifying Self-Immolative Nanoparticles for Drug Delivery* **Elizabeth Gillies**, Western University
3:00	*2:50-3:10* *Biomarker Testing in Lung Cancer* **Ming Tsao**, Ontario Cancer Institute *3:10-3:30* *Tumor Mutational Burden as a Biomarker for Cancer Immunotherapy* **Caitlin Connelly**, Foundation Medicine	*Growing up High: Long-Term Consequence of Adolescent Cannabis Use - Preclinical Studies* **Jibran Khokhar**, University of Guelph	*Polymer- Based Protein Delivery Systems* **Sankaran Thayumanavan**, University of Massachusetts
3:30	***Coffee & Tea Break: Posters, Exhibitors, & Networking***		
4:00	*4:00-4:20* *Molecular Diagnostic Advancement in Oncology* **Alan Spatz,** McGill University & Jewish General Hospital	*Adolescent Cannabis Use: Risk for Mental Health and Drug Dependence* **Marcus Munafò**, University of Bristol, UK	*Controlled-Release Nano-Therapeutics: The Status of Translation* **Subramanian Venkatraman**, NTU Singapore
4:30	4:20-5:00 Panel Discussion: All Speakers + **Janet Dancey**, Canadian Cancer Trials Group, and Queens University **Raffi Tonikian**, Merck	*Opioid Sparing Effects of Cannabinoids: Myth or Reality?* **Bernard Le Foll**, University of Toronto	*Biomimetic Nanoparticles for Targeted Drug Delivery and Detoxification* ***Liangfang Zhang**, UC San Diego*
5:00 PM	*5:00-5:10 PM* **Selected CSPS oral abstract presentation:** *Combining Statins with Radio-immunotherapy as a Novel Therapeutic Strategy for Colorectal Cancer* **Vessie Vassileva**, Imperial College London	*5:00-6:00 PM* - **Panel Discussion** ***The Future of Medical Cannabis in Canada*** *Moderator: James Evans, University of Toronto* **Participants:** • **Beleave** (Peter Chen, VP of Science and Technology) • **Avicanna** (Aras Azadian, President) • **CannTrust** (Kaivan Talachian, VP, Professional Services) • **University of Toronto** (Lakshmi Kotra)	*5:00-5:10 PM* **Selected oral abstract presentation:** *Hyperthermia-mediated Drug Delivery Increases Cisplatin Sensitivity and Accumulation Resulting in improved Efficacy in Triple Negative Breast Cancer* **Michael Dunne**, University of Toronto **Presentation of CC-CRS Poster Awards**
6:30 PM	***Conference Gala and Awards Dinner*** *(6:30 PM Cash Bar, 7:30 PM Dinner)* *Churchill Ballroom*		

FRIDAY, MAY 25 - MORNING SESSIONS		
7:30 AM	***Registration***	
8:00 AM	***Coffee & Muffins***	
8:30 - 9:30	**PLENARY SESSION:** **Richard Weinshilboum**, Mayo Clinic *Pharmacogenomics: Clinical Implementation and Future Challenges* *Chair: Micheline Piquette-Miller, University of Toronto* Room: Churchill Ballroom	
9:30--10:00	***Coffee & Tea Break: Networking***	
10:00 - 12:00 Noon	**SESSION 5A: PHARMACOGENOMIC IMPLEMENTATION** *Chair: Micheline Piquette-Miller, University of Toronto* Room: Churchill Ballroom	**SESSION 5B: DRUG THERAPY IN CHILDREN** *Chair: Michael Rieder, Western University* Room: Rosetti
10:00	*PRIME: Implementing Pharmacogenomic Testing into Pharmacy Practice - Focus on Mental Health Pharmacotherapy* **Natalie Crown**, University of Toronto	*Nephrotoxic Acute Kidney Injury in Hospitalized Children and Description of a National Cisplatin Pediatric Cohort* **Mike Zappitelli**, The Hospital for Sick Children, Toronto
10:30	*Clinical Pharmacogenomics Program in Pediatric Oncology: 225 Patients and Counting* **Bruce Carleton**, University of British Columbia	*Novel Approaches to Improving Pharmacotherapy in Epilepsy: Machine Learning and Human Organoids* **Peter Carlen**, University of Toronto
11:00	*Clinical Utilization of Pharmacogenomic Testing – The Evolving Canadian Environment* **Christopher Trevors**, Dynacare	*Vaccinating Children Against Pain and Fear* **Anna Taddio**, University of Toronto
11:30	*Pharmacogenetics in the Benefits Arena – Baby Steps; Giant Opportunities* **Wayne Murphy,** Prudent Benefits Administration Services	**CSPT Senior Investigator Award:** *Addiction to Cocaine: How you Take the Drug is More Important than how Much* **Anne-Noël Samaha,** Université de Montréal
12:00 PM	***Trainee Poster Awards - Announcement and Presentation of Awards*** Room: Churchill Ballroom	
12:30 PM	***Conference Concludes***	

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CANNABINOIDS

PANEL DISCUSSION:

PANEL MEMBERS

Avicanna: Aras Azadian, President

Beleave: Peter Chen, Vice President of Science and Technology

CannTrust: Kaivan Talachian, Vice President, Professional Services

University of Toronto: Lakshmi P. Kotra, B. Pharm.(Hons), Ph.D.

SESSION 4C:

INNOVATIVE BIOMATERIALS FOR DRUG DELIVERY

FRIDAY, MAY 25

PLENARY SESSION 4

SESSION 5A:

PHARMACOGENOMIC IMPLEMENTATION

SESSION 5B:

DRUG THERAPY IN CHILDREN

POSTER SESSION 1 - CSPS AND CC-CRS
WEDNESDAY, MAY 23

Biomedical Sciences

Clinical Sciences & Pharmacy Practice

Drug Delivery and Pharmaceutical Technology

POSTER SESSION 2 - CSPS AND CC-CRS
THURSDAY, MAY 24

Biomedical Sciences

Clinical Sciences & Pharmacy Practice

Drug Delivery and Pharmaceutical Technology

Pharmaceutical and Analytical Chemistry

Pharmacokinetics and Pharmacodynamics

POSTER SESSION 2 - CSPT
THURSDAY, MAY 24

Invited Speaker Abstracts & Bios

Tuesday, May 22

Industry Day:

Innovation and Management of Modern Pharmaceuticals

PLENARY SESSION 1

Mary Haak-Frendscho, Blueline Bioscience

Chairs: Andrew Casey, BIOTECanada, and Christine Allen, University of Toronto

The View from Here: Innovation Canadian Style

Mary Haak-Frendscho, CEO, Blueline Bioscience; and Venture Partner, Versant Ventures, Toronto

This presentation will provide an investor perspective on the Canadian innovation ecosystem, as seen through a US biotech lens. What we see, filling the gaps and leveraging our unique strengths. The talk will wrap up with a Q&A session.

Mary Haak-Frendscho

Mary is CEO of Blueline Bioscience in Toronto and a Venture Partner with Versant Ventures. Previously, she established and served as Chairman of Compugen, Inc., was CEO and member of the Board at Igenica Biotherapeutics, Inc., and established and was President, Chief Scientific Officer and Board member of Takeda San Francisco. Mary began her industry career at Genentech, where she played a key role in the development of omalizumab (Xolair®) for the treatment of severe asthma and CIU.

Presentations

Session Chair: Andrew Casey

Andrew Casey became president and CEO of BIOTECanada in August, 2012. In his role as President & CEO of BIOTECanada Andrew is responsible for the strategic operations of the Association representing Canada's biotechnology sector. As the head of BIOTECanada, he is the lead spokesperson for Canada's biotechnology industry communicating on the industry's behalf with government, regulators, international bodies, media and the Canadian public.

In his capacity as head of BIOTECanada Andrew also serves as:

- Director, Board of Directors, BIOTECanada
- Vice Chair, International Council of Biotechnology Associations (ICBA)
- Director, Board of Directors, Institute for Research in Immunology and Cancer, Commercialization of Research (IRICoR)
- Director, Board of Directors, Arthritis Alliance of Canada (AAC)

Prior to joining BIOTECanada, Andrew served from 2004-2012 as Vice President, Public Affairs and International Trade with the Forest Products Association of Canada (FPAC). From 1993-2004 he was the Assistant Vice-President, Government Relations with the Canadian Life and Health Insurance Association. Between 1989 and 1993 Andrew worked on Parliament Hill as a political advisor in the office of the Federal Ministry of Finance.

Andrew Casey is a native of Montreal, Quebec. After attending Loyola High School (Montreal) and St. Lawrence CEGEP (Quebec City) he graduated from Carleton University (Ottawa) with degree in Political Science.

MaRS Innovation: Modern Approaches to Bridging the Valley of Death

Raphael (Rafi) Hofstein, President & CEO, MaRS Innovation

MaRS Innovation (www.marsinnovation.com; @marsinnovation) is a leading provider of commercialization services, early-stage funding, and deal-brokering with industry and private investors. As a member-based organization made up of 15 member institutions, our mandate is to drive the commercialization of their most promising research breakthroughs. MaRS Innovation's portfolio consists of early-stage assets and companies, and we leverage our deep expertise and experience to mature this portfolio via important global and strategic partnerships. With an active portfolio of more than 40 companies which have raised in excess of $250M from global investors, and with the creation of more than 400 direct jobs, MaRS Innovation is truly a leader in the commercialization field.

MaRS Innovation provides the important – and unfortunately, most often non-existing – bridge between initial concept development and the acceleration towards a more mature market-ready state. Nascent scientific technologies have very few avenues of assistance in crossing the "valley of death" – this is where we come in, by addressing this challenge through company creation and formation of an ideal R&D platform that is attractive to industry.

MaRS Innovation is finding novel ways to ensure a faster and more certain path to better commercialization of these young scientific discoveries. By creating meaningful collaboration, locally and globally, with industry partners – such as LAB150 with Evotec AG, and UTEST with University of Toronto (www.lab150.com and www.utest.to) to name but two examples of recent partnerships – MaRS Innovation is laying the foundation to successfully launch start-up companies. To this end, we have developed a "Venture Builder" process as a means to attain improved technology development, post ideation.

Dr. Hofstein will discuss these and other novel and innovative commercialization initiatives undertaken by MaRS Innovation as the organization continues to find ways to navigate an ever- changing start-up landscape with the aim to bringing its member discoveries to market quickly and fruitfully.

Raphael (Rafi) Hofstein

Dr. Hofstein joined MaRS Innovation in 2009 after past positions that include Scientific Director of Biotechnological Applications Ltd.; Manager R&D and Chief of Immunochemistry at the International Genetic Scientific Partnership; Scientific Director of the Israeli office of Ecogen Inc.; Vice President, Business Development for Ecogen in Langhorne, Pa.; and President and CEO of Hadasit, the commercialization company of Hadassah, the largest teaching hospital in Israel.

Dr. Hofstein received his PhD and Master of Science degrees in Life Sciences and Chemistry from the Weizmann Institute of Science in Rehovot, Israel.

JLABS @ Canada Catalyzing Innovation

Allan Miranda, Johnson & Johnson Innovation, JLABS in Canada

JLABS represents a new type of incubator in the Canadian ecosystem. Located in the heart of Toronto it provide emerging companies the opportunity to access state-of-the-art technology, venture capital investors, unique programming and mentorship. This is all accomplished with a no-strings attached model in that intellectual property rights are neither shared nor are there any rights of first refusals. Biotech entrepreneurs are afforded the opportunity to reach their development milestones and grow their companies unfettered by ties to a larger corporate entity. Increasing the number of biotechnology companies in Canada will have a benefit to the economy by providing jobs and the next wave of cutting edge technologies. Ensuring these technologies get to patients faster means that biotechnology companies and regulators need to work together earlier in development to ensure innovation, patient safety and value are adequately captured in clinical development programs.

Allan Miranda

As Head of Johnson & Johnson Innovation, JLABS in Canada, Allan is responsible for external engagement, innovation sourcing, company onboarding, portfolio management, operational excellence, educational programming and P&L. He catalyzes and supports the translation of science and technology into valuable solutions for patients and consumers across the pharmaceutical, medical device, consumer and healthtech sectors.

Allan joined the JLABS team from Janssen Canada, where he has spent the last 12 years in positions of increasing responsibility in business development, marketing and market access. His most recent role was Therapeutic Lead Immunology and Primary Care where he was responsible for market access strategy for a complex product portfolio exceeding $1 billion. Allan started his career at PARTEQ Innovations, the technology transfer arm of Queen's University at Kingston where he was responsible for technology assessment and new company start-up. He then moved to Paladin Labs, where he successfully completed numerous in-licensing transactions for specialty pharmaceutical products for the Canadian market. Allan subsequently worked in business development for two early stage biotechnology companies in Canada leading their business development and partnering initiatives prior to joining Janssen.

Allan received his Ph.D. in Neuropharmacology from Queen's University at Kingston, Ontario and his MBA from McGill University in Finance and Strategy.

Avicanna and Evidence Backed Delivery of Medical Cannabis

Aras Azadian, Chief Executive Officer and Co-Founder, Avicanna, Toronto, ON

With a strictly scientific and medical focus, Avicanna has optimized its vertically integrated value chain and has positioned itself for the future of the medical cannabis industry. This presentation will take a brief look into Avicanna's four major divisions including i) the organic cultivation project in Colombia; ii) the research and product development at JLABS @ Toronto and the University of Toronto; iii) the clinical development partnerships in Canada; Jamaica and Colombia, and iv) Avicanna's commercial product offerings. Avicanna's cultivation projects take advantage of the optimal growing conditions of Santa Marta, Colombia where selective breeding and genetic techniques are used to cultivate plants expressing specific cannabinoids of varying proportions for medical purposes. The proprietary extraction and isolation processes used, result in purified natural and organic cannabinoids that are further characterized to pharmaceutical grade quality. In collaboration with several leading research and medical institutions including, the University Health Network (UHN) and Dr. Christine Allen's Research Group (CARG) at the University of Toronto, Avicanna's team of expert scientists are studying the medical properties of cannabinoids and the potential benefits they may provide to specific indications. Avicanna is also using its collaborative relationships to explore and develop advanced cannabinoid formulations and delivery mechanisms. Finally, Avicanna is entering clinical development stage where several of their products will be undergoing human trials with some of the major hospitals and institutions across three countries. Avicanna is uniquely positioned to address the current gaps in the medical cannabis industry due to its rigorous evidence and scientific-based approach that bring rationally designed and clinical meaningfulness to their cannabinoid products.

Aras Azadian

Aras is the chief executive officer and a co-founder of Avicanna, and brings with him extensive senior management experience in the biotechnology and financial sectors including his involvement in several successful start-ups. In addition to his international experience in corporate development his diverse roles included his position as the president of an investment corporation in the cannabis space and former COO of an oncology company. Aras has degree in economics from York University in Toronto and MBA from EADA Business School in Barcelona.

Structure-Based and AI-Augmented Proteome Screening for Drug Discovery

Stephen MacKinnon, PhD, Director of Research and Development, Cyclica Inc.

Cyclica has developed Ligand Express, an innovative and patented AI-augmented platform that efficiently screens small molecule drugs against the entire known proteome via cloud computing to determine on- and off-target protein-drug interactions thereby enabling *in silico* polypharmacology. The platform is used by medicinal chemists, biologists, drug screening groups, and others to identify drug targets, to investigate the mechanism of drug action, to prioritize leads, and to reposition / repurpose assets. Ligand Express can securely incorporate proprietary structure- and bioassay data from clients to augment findings that are generated using large public

datasets. The company has recently developed a patented biophysical and AI-assisted Multi Targeted Drug Discovery (MTDD) technology to generate new chemical entities (NCE) *in silico* using a differential drug design strategy, and they have also developed structural pharmacogenomic (SPGx) capabilities that enable the mapping of genetic information onto protein structures, which will lead to a better integration between genomics and drug discovery. With developments such as MTDD and SPGx Cyclica has evolved from a company with a "proteome screening" technology into one with an integrated network of technologies to support a design --> screen --> personalize workflow based on a foundation of polypharmacological profiling.

Stephen MacKinnon
Stephen received his PhD in Biochemistry from the University of Toronto, using structural bioinformatics to study systemic trends in protein structures to reveal new mechanistic insights. At Cyclica, he designed and led the development of computational proteome screening technologies. Stephen now oversees the prototype stages of new scientific computing solutions and partnered research projects using predictive informatics.

From the Bench to the Board Room: The Things Nobody Tells You

Shawn H. Glinter, Founder & CEO, Pendant Biosciences

You're gonna want to hear this one! Come listen to Shawn Glinter, a successful serial entrepreneur in the healthcare, technology, and life sciences space. Shawn will share his journey that started over 20 years ago and the roller coaster ups & downs of launching startups. You will hear Glinter share his current startup journey, the decision to launch the business; along with some of the 'crazy things' that you never believe will happen.

Shawn will discuss his challenges as an entrepreneur, along with both the successes and hurdles that he and his team have encountered. You'll hear about the "Oh-Sh*t" moments of starting a life science's company and some of the current success that the company has achieved to date.

It's a jam packed 15-minutes, so come out and meet Shawn and learn more about the exciting times he's pursuing with Pendant Biosciences. You'll likely leave with some great advice and pearls of wisdom…whether you're pursuing industry, academia, and most definitely the startup life.

Shawn H. Glinter
For over 20 years, successful serial entrepreneur Shawn Glinter has been in love with helping students, faculty & entrepreneurs with their startups and early stage company's. His background reveals a vast experience and explains the passion he's shown as he has helped, advised, and worked with over 9 dozen first time founders of startups and mentored over 1000's of companies.

Shawn's career began in emergency medicine and hospital administration (George Washington University Health System and MedStar Health in Washington, DC, and Vanderbilt University in Nashville, TN).

Most recently, Shawn was a co-founder & CEO of a life sciences (water technology) company for an entity located in the USA, Canada, and Europe. In just over 3.5 years he successfully grew that company from $600K to 11M (which eventually sold). Shawn is currently the Founder & CEO of the biotechnology startup Pendant Biosciences (formerly Nanoferix) an advanced materials company developing innovative surface coating and drug delivery technologies using a unique, polymer-based platform. Pendant is currently a Johnson & Johnson Innovations JLABS Company.

Shawn recently received a Faculty appointment at the University of Louisville, Schools of Medicine, in the Department of Neurological Surgery, as the Director of Innovation & Entrepreneurship. Shawn is currently the Entrepreneur in Residence at Belmont University and a Mentor in Residence at Vanderbilt University in Nashville, TN. Shawn has spent the last 10 years as one of the Master Mentors at the Nashville Entrepreneur Center. He also a mentors for the Life Science Tennessee Mentor Program, the JumpStart Foundry, the Co.Lab accelerator program in Chattanooga, and is a Master Mentor for Launch TN (a state wide accelerator program).

Shawn is married to his wife Nicole and they have a 10-year-old boy, Jordan. "I love being a Dad, Husband, and Entrepreneur every day of my life."

Navigating the Cannabis Pharma Space

Melanie E.M. Kelly[1] & Guy Chamberlain[2]
[1]Panag Pharma Inc. Halifax, Nova Scotia and [2]Tetra Bio-Pharm, Orleans, Ontario

Panag Pharma Inc. (Panag) was formed in 2014. The founders of Panag, all clinician researchers and scientists, have built on their experience and foundation in the cannabinoid space since the middle of the 90's and leveraged that experience into a series of innovative pharmaceutical products that fill a niche in the chronic pain market. Current pain management therapies lack efficacy and safety and have proved inadequate for treatment of chronic pain and neuropathic pain conditions. The emergence of cannabis-based research demonstrating efficacy in chronic pain management and a changing regulatory environment have opened up significant opportunities to address this medical need. The goal of Panag is to develop safe and effective products for chronic pain and inflammation to a proof of concept stage and then licence to a qualified partner. An example of this is the current partnership between Panag and Tetra Bio-Pharma (Tetra), the licensing partner for Panag's topical and ocular cannabinoid pain products. In the Panag-Tetra partnership, Tetra provides non-dilutive funds to develop the licensed drugs to proof of concept and a commitment to cover costs tor each commercialization. Importantly, Tetra brings a team of people who know the regulatory space extremely well and understand the ability to work with regulatory agencies. This presentation examines how partnerships between academic start-up drug companies and industry partners can pool complimentary expertise to exploit current regulatory and market opportunities in the development of cannabinoid drugs for areas of medical need.

Melanie Kelly
Dr. Melanie Kelly is Professor of Pharmacology, Ophthalmology & Visual Sciences, Anesthesia, Perioperative Medicine and Pain Management, Dalhousie University, Nova Scotia, Canada. Professor Kelly is also the Executive Director of the International Cannabinoid Research Society, a Canadian Consortium for the Investigation of Cannabinoids Board Member and Director and Chief Scientific Officer, Panag Pharma Inc. Halifax, Nova Scotia, Canada. Dr. Kelly's primary research expertise is in translational pharmacology and drug discovery. Her research specifically addresses the pharmacology of the endocannabinoid system and how cannabis and cannabinoids can modify disease. She has published more than 100 publications in the area of pharmacology, cannabinoids and the endocannabinoid system and holds several patents in the area of cannabinoid drugs for therapeutic management of disease. Professor Kelly has participated in and developed curriculum in medicine and pharmacy at undergraduate and graduate levels as well as content for continuing medical education and postgraduate professional education. She contributes as an expert consultant to industry with regard to drug development in the cannabis/cannabinoid space and in the development of scientific material for public dissemination and knowledge translation. Dr. Kelly's recent work has focused on development of new therapies to alleviate pain and inflammation. As one of the founders of a small drug company based in Halifax, she is working to leverage research discoveries into Health Canada approved medicines for those suffering from chronic neurodegenerative diseases.

Guy Chamberland
Dr. Guy Chamberland, M.Sc., Ph.D., M.H., has been Chief Scientific Officer & Regulatory Affairs of Tetra Bio-Pharma since June 2016. He has been Vice President of Regulatory Affairs & Product Development at Biotanika Health Group Inc. since March 2007. He served as Vice President of Clinical & Regulatory Affairs at Victhom Laboratory Inc. from 2005 to 2007. He developed a specialty in regulatory affairs (drugs, biologics, medical device, combination products, botanicals). He works closely with physicians and naturopathic physicians in these clinical areas. He spent 6 years as the Co-Chair and member of Health Canada's Expert Advisory Committee for Veterinary Natural Health Products and Low Risk VHP. He was the Program Director of MDS Pharma Services. Dr. Chamberland has over 10 years experience in the development of clinical research protocols for botanical medicines and the management of these clinical studies in the areas of anxiety, sleep, pain, depression, inflammation and wound healing. He has over 23 years' experience in the development of new drugs in the pharmaceutical industry (Canada and USA). He was a member of the Investment Committee of Fonds Bionovation for 7 years. Since 2007, Dr. Chamberland developed an expertise in the development of botanical medicines.

Phytoglycogen Nanoparticles in Nanomedicine: Novel Delivery, Anti-infective and Immuno-modulatory Agents

John Dutcher, Founder, Mirexus Biotechnologies/ Glysantis

Phytoglycogen is a highly branched polymer of glucose that is produced in the form of dense, monodisperse nanoparticles by some varieties of plants such as sweet corn. Its special tree-like or dendrimeric structure combined with its natural, safe profile make the particles highly desirable for applications involving the human body, such as personal care, nutrition and biomedicine. I will describe promising results for the use of the NanoDendrix technology as novel delivery, anti-infective and immunomodulatory agents, and our journey from the initial serendipitous discovery of the particles to the commercialization of this natural, sustainable nanotechnology in our Guelph-based spinoff companies Mirexus Biotechnologies and Glysantis.

John Dutcher
John Dutcher is the Senior Canada Research Chair in Soft Matter & Biological Physics at the University of Guelph and a Fellow of the American Physical Society. He has held leadership roles at the University of Guelph (Director, Centre for Food and Soft Materials; Director, Nanoscience Program) and in the national Networks of Centres of Excellence (Theme Leader, Advanced Foods and Materials Network). He is a Founder of Mirexus Biotechnologies and its biomedical subsidiary Glysantis, which are commercializing a natural, sustainable nanotechnology for use in personal care, nutrition and biomedical applications. For the development of this technology, he received the 2017 University of Guelph Innovation of the Year award.

Nacellins: New Therapeutic Entities for Challenging Targets

Jeffrey Coull, President and CEO, Encycle Therapeutics

Encycle Therapeutics is a Toronto-based drug discovery company exploiting a proprietary chemistry to synthesize more drug-like peptide macrocycles. These so-called “nacellins” can be generated at sizes greater than 500 Da without compromising properties including permeability and oral bioavailability. Dr. Coull will discuss the emergence of this new technology and how Encycle is applying it to challenging protein targets.
Jeffrey Coull
Dr. Jeffrey Coull is the President and CEO at Encycle Therapeutics. Prior to holding this position, he was head of operations at the Ontario Brain Institute, and before this, held the position of President and CEO at Chlorion Pharma. He is trained as a pharmacologist and has made significant contributions to the field of pain neuroscience.

Targeting the Cancer Cell Secretome to Overcome Tumor Heterogeneity

Anton Neschadim, PhD MBA, CEO, ImmunoBiochem Corporation

Surface-expressed tumor targets tend to have distributed and heterogeneous expression in solid tumors, subject to both intra-patient and inter-patient heterogeneity. This heterogeneity is limiting the efficacy of targeted biologics and leading to rapid generation of resistance. In contrast, the tumor microenvironment is a rich, under-explored source of tumor targets that are present in various solid tumors more consistently and homogenously than surface-expressed targets. Of particular interest to ImmunoBiochem are targets that are amplified in tumor cell secretomes. The endosomal-lysosomal system of cancer cells undergoes striking changes on transformation, such as failure by cancer cells to properly organize their intracellular compartment and acidify lysosomes. These changes underlie tumor progression and metastasis in advanced cancers. As a result, the secretomes of cancer cells are often enriched in proteins and protein variants that are only found in the tumor microenvironment and are distributed homogenously throughout the tumor mass. They are also interacting with various components of the tumor microenvironment in addition to the tumor cells, including tumor-supporting stroma and tumor-infiltrating macrophages. These secretome-based proteins engender a novel class of selective tumor targets that could be leveraged to eradicate tumors with potentiated biological therapeutics, such as the highly potent antibody-drug conjugates (ADCs). ImmunoBiochem’s novel therapeutics are tumor-microenvironment-targeted armed antibodies

capable of targeting many different solid tumors and are not constrained by the expression of the target on cancer cells like conventional antibodies and ADC therapeutics. They have highly selective activity in vitro and in vivo, damaging tumors but sparing normal, healthy tissues, and are capable of addressing the challenge of inherit and acquired tumor heterogeneity in cancer therapy.

Anton Neschadim

Anton is a biomedical professional, scientist, innovator, entrepreneur and venture capitalist with 15 years of industry and academic experience in research and drug development. At ImmunoBiochem Corporation, Anton is leading the development of a new class of tumor microenvironment-targeted anti-cancer therapeutics. Anton was formerly the Director of Drug Development at Armour Therapeutics Inc., a biopharmaceutical company developing a new class of anti-cancer therapeutics for prostate, breast and ovarian cancers. Throughout his career, Anton worked on R&D and consulting projects with several biopharmaceutical companies developing biological therapeutics and immunotherapies in oncology. Anton has expertise in cancer research, immunology, chemistry, regenerative medicine and gene therapy, and authored more than 25 peer-reviewed publications and patents.

Anton obtained his PhD, MSc, and Hon. BSc degrees in medical biophysics, immunology, and biological chemistry at the University of Toronto, where he also completed postdoctoral work and his MBA at the Rotman School of Management. Anton is also a graduate of the CIHR Training Program in Regenerative Medicine (TPRM), Toronto General Hospital, University Health Network. Anton was a founding board member, and former CCO and organizing committee member of the Canadian Science Policy Centre (Toronto, ON) – a national organization promoting science policy in Canada.

Improving Immune Responses to Cancer Antigens Using a Nanoparticle Formulation that Targets Lymph Node Cells

Genevieve Weir, Director of Research, IMV Inc.

IMV Inc. has developed a novel lipid in oil based delivery platform that can specifically target immune cells. This technology, called DPX, has been used to develop DPX-Survivac, which contains short peptide epitopes derived from the tumour associated antigen survivin. Treatment with DPX-Survivac results in robust and sustained T cell responses in ovarian cancer patients. DPX-Survivac is being evaluated in Phase 1 and 2 clinical trials in combination with other immune modulating agents, such as Incyte's IDO inhibitor (epacadostat) and Merck's anti-PD-1 (pembolizumab). Based on preclinical testing, these combinations have the potential to improve patient outcome by programming the immune system and activating a targeted T cell mediated immune response towards the tumour. The unique mechanism of action of DPX has been explored using magnetic resonance imaging (MRI) to monitor the clearance of various components of the treatment which can be labeled with SPIO. This work has shown that DPX does not support passive release of components in the formulation, rather they are held at the site of injection and actively removed up by immune cells, which bring them directly to the lymph nodes. Ultimately this results in potent T cell activation and infiltration of tumours with these T cells. This has been recognized as a key step for successful immune therapy of cancer, and is complimentary to many other forms of immune therapies.

Genevieve Weir

Genevieve Weir, PhD, is the Director of Research at IMV Inc. and has been with the company for 12 years. Dr. Weir oversees translational research activities at IMV, bringing discoveries from concept to clinical development. She works closely with the Product Development and Clinical teams at IMV to conduct translational research. Her work involves developing new models and assays, preclinical testing of treatments, evaluation of immune responses in preclinical and clinical testing. Dr. Weir received her PhD from Dalhousie University in Microbiology and Immunology, and she has co-authored several patents and publications through her work with IMV.

Wednesday, May 23

Trainee Breakfast

Chair: Nana Lee, University of Toronto

Creating Your Career Path with your Grad Degree

Nana Lee, PhD, Director and Lecturer of Graduate Professional Development, Departments of Biochemistry and Immunology, Lead Coordinator, Faculty Development Program, Graduate Life and Science Education, Faculty of Medicine, University of Toronto

How do you develop core competency skills during graduate school which empower you to be market-ready?
How do you find the hidden job market?
How do you strengthen strategic communications to create the job?
These are the highlights of this trainee workshop, led by the internationally recognized Dr. Nana Lee, Director of Graduate Professional Development (GPD) programs at the Departments of Biochemistry, Immunology, and Faculty of Medicine, University of Toronto. She has spoken to over 1000 students, faculty and industry professionals with her GPD curriculum-embedded course featured in Science Careers, the National Post, Conference Board of Canada, and the Council of Graduate Schools.

Nana Lee
Dr. Nana Lee holds a PhD from U of Toronto, a visiting scholar experience from MIT, and a postdoctoral fellowship from the University of Michigan. She brings her years of experience and expertise from the biotech industry (Ellipsis Biotherapeutics, DNA Software) into the classroom with her internationally recognized (Science Careers, Council of Graduate Schools\NSF, Conference Board of Canada) graduate-level professional development curriculum-embedded course in the Departments of Biochemistry and Immunology. She has spoken to over 1000 students, postdocs, faculty and curriculum administrators in empowering trainees to be market-ready for any career.

Wednesday, May 23

PLENARY SESSION 2

David Juurlink, Sunnybrook Health Sciences Centre

Chair: Tuan Trang, University of Calgary

The North American Opioid Crisis from 30,000 Feet

David Juurlink, Sunnybrook Health Sciences Centre

Objectives:

- To review the genesis and recent evolution of the opioid crisis
- To discuss its current scope
- To review ways in which the crisis might be mitigated

David Juurlink

Dr. Juurlink is the Eaton Scholar and Professor of Medicine, Pediatrics and Health Policy at the University of Toronto. He is head of the Division of Clinical Pharmacology and Toxicology at both Sunnybrook Health Sciences Centre and University of Toronto, and a medical toxicologist at the Ontario Poison Centre. He is also a senior scientist at the Institute for Clinical Evaluative Sciences, where he maintains an active research program in the field of drug safety.

Wednesday, May 23

SESSION 1A:

Opioid Crisis

Chair: David Juurlink, Sunnybrook Health Sciences Centre

Opioid Use and Adverse Events: Emerging Trends and Policy Impacts

Tara Gomes, St. Michael's Hospital

Canada and the United States have the highest prescription opioid consumption per capita in the world, which has been attributed to widespread overprescribing of this class of medications for decades. In parallel with increasing opioid prescribing, rates of opioid-related overdoses have climbed across North America, leading to many characterizing the opioid-related harms as the most important public health issue of our time. In 2017, it is anticipated that there will be more than 4000 opioid-related deaths in Canada; however, as policy and clinical response to this issue has evolved over the past decade, so have the drivers of this epidemic. In particular, as prescription opioids become more difficult to access, several provinces across Canada have demonstrated rising rates of fatal overdoses from illicitly manufactured opioids, such as fentanyl and its analogues. This presentation will review patterns of opioid prescribing and related harms across Ontario, and will speak to the impacts of recently introduced policies designed to address this issue, focusing both on intended and unintended consequences. Finally, the implications of the shifting opioid environment will be discussed, along with suggestions for how future policies and responses to this issue can be designed to effect positive change.

Tara Gomes
Dr. Tara Gomes is an epidemiologist and Principal Investigator of the Ontario Drug Policy Research Network (ODPRN), a provincial network of researchers with expertise in pharmaceutical utilization, outcomes and policy who rapidly conduct research for drug decision-makers in Ontario and across Canada. She is also a Scientist in the Li Ka Shing Knowledge Institute of St. Michael's Hospital and the Institute for Clinical Evaluative Sciences and an assistant professor at the University of Toronto. Her research is focused on pharmacoepidemiology, drug safety and drug policy research leveraging large, administrative databases, and she has published over 125 peer-reviewed articles and over 50 policy reports in this area.

Dr. Gomes has worked closely with the Ontario Ministry of Health and Long-Term Care and the Canadian Network for Observational Drug Effect Studies (CNODES) to develop evidence to inform policies related to opioid use and abuse in Ontario and more broadly across Canada. She has also served as an expert for the US Food and Drug Administration and the US Department of Transportation in discussions related to opioid policies and regulations. In 2014, the ODPRN was awarded the Institute for Public Administration of Canada's Bronze Public Sector Leadership Award in Health and Education.

Pharmacological Strategies for Harm Reduction in Opioid Use Disorder: An Overview

Jessica L.S. Leen, MD, FRCPC, University of Toronto

This talk will provide a brief overview of the pharmacologic harm reduction strategies currently used in the management of opioid use disorder. These include, but are not limited to, opioid agonist therapies (methadone, buprenorphine, sustained release oral morphine, intravenous prescription grade heroin and hydromorphone) and opioid antagonists (naloxone and naltrexone). Other objectives include reviewing basic harm reduction principles and the neurobiologic model of addiction. Attendees will develop a working knowledge and understanding of the key pharmacological principles supporting these strategies.

Jessica L.S. Leen
Jessica L S Leen is a Royal College of Physicians and Surgeons of Canada certified general internist who completed her core training and medical school at the University of Toronto. She is currently completing her final year of her internal medicine subspecialty fellowship in Clinical Pharmacology and Toxicology. Her areas of focused interest include addiction medicine, specifically opioid substitution therapies, therapeutic use of cannabinoids as opioid-sparing agents, and adverse drug reactions. Her career goals include improving the care of the patient with addictions and promoting the value of clinical pharmacology in the community.

Nudges, Pushes, Policy and St Francis: Perspectives on the Opioid Crisis

Shawn Bugden, Memorial University of Newfoundland / University of Manitoba

The opioid crisis rightly dominates the headlines as clinicians, policy makers and politicians all struggle to find solutions. Linked administrative databases give us the ability to assess aspects of the impact policy changes on opioid prescribing. This presentation will review impact of a variety of policy changes and the apparent impact on practice in Manitoba. Manitoba has had one of the most regulated opioid prescribing environments in the country for more than 20 years. Consideration will be given to the impact of tamper resistant products policy, exempted codeine products policy, drug safety warnings and opioid guidelines. Perhaps there is some positive news to share, as we continue to address this dire crisis.

Shawn Bugden
Shawn is Dean of the School of Pharmacy at Memorial University of Newfoundland. He is a recent transplant from the Rady Faculty of Health Sciences at the University of Manitoba where he taught ethics, biostatistics and critical appraisal. His research focusses on drug evaluation, evidence-based healthcare, pharmacoeconomics and pharmacoepidemiology. Shawn is a graduate of the College of Pharmacy at the University of Manitoba and has taken further post-graduate training at Oxford University, and the University of Washington.

HPFB Activities in Support of the Federal Action on Opioids

Emma Spreekmeester, PhD., Manager / Health Products and Food Branch, Health Canada

The growing number of overdoses and deaths caused by opioids is a national public health crisis. The opioid crisis can be linked to the rapid rise in rates of drug overdoses and death involving both prescription opioids and increasingly toxic illegal drugs due to the increased presence of powerful illegal substances, such as fentanyl, a drug 50-100 times more potent than morphine. The Federal Minister of Health has made addressing this crisis a top priority. This is a complex health and social issue that needs a response that is comprehensive, compassionate and evidence-based. Health Canada is working with provinces, territories and other partners across the country to take a collaborative approach to the crisis. Under the 'Joint Statement of Action to Address the Opioid Crisis', Health Canada committed to take new action across the Health Portfolio related to prevention, treatment, harm reduction and enforcement measures, all supported by a strong evidence base.

Emma Spreekmeester
Emma Spreekmeester is the manager of the Central Nervous System Division 1 (CNSD1) at the Therapeutic Products Directorate (TPD) of Health Canada. She joined Health Canada in 2005 and worked as a drug reviewer until 2014, when she assumed the manager position in the CNS Division. During her career at Health Canada, Emma has participated actively on several internal regulatory committees, addressing topics such as Women in Clinical Trials, Orphan Drugs, the Importation of Drugs for an Urgent Public Health Need and various aspects of Health Canada's Opioid Action Plan. Emma completed both her Ph.D. in Neurology and Neurosurgery and her M.Sc. in Psychiatry at McGill University, in Montreal, Quebec.

Wednesday, May 23

SESSION 1B:

Regulatory Reforms

Co-Chairs: Catherine Parker, Health Canada

Improving Access to Innovative Medicines: Health Canada's Regulatory Reform Initiative

Catherine Parker, Director General, Biologics and Genetic Therapies Directorate, Health Canada

In 2016, Canadian provincial, territorial and federal health ministers committed to work together to improve the affordability, accessibility and appropriate use of prescription drugs. The government commitment to improving drug access has been reinforced by significant funding in the 2017 federal budget to Health Canada (the federal drug regulator), the Canadian Agency for Drugs and Technologies in Health (a health technology assessment organization), and the Patented Medicines Price Review Board (which ensures that prices on patented medicines are not excessive). Part of this investment is driving a large-scale Health Canada transformation over the next five years of how the various systems and players work together to bring therapeutic products to market.

This initiative, called the Regulatory Review of Drugs and Devices (R2D2), consists of regulatory and policy changes to improve timely access to safe drugs for patients, including accelerated market access to innovative technologies coming to market. R2D2 began in 2017, and a variety of projects attacking the problem of drug access have been developed, under the pillars of expanded collaboration with health partners, more timely availability of drugs and devices, and enhanced use of real world evidence. Expected outcomes of this initiative include agile regulatory pathways that support the drugs needed most by the healthcare system coming to market, better alignment and partnerships between the various players involved in bringing therapeutic products into the healthcare system and better support for the health needs of Canadians. An overview of the R2D2 projects, future directions, and progress made to date will be provided.

Catherine Parker
Catherine Parker was appointed Director General of the Biologics and Genetic Therapies Directorate (BGTD) of the Health Canada in June 2015. Ms. Parker was previously the Director of its Office of Policy and International Collaboration where she played a key role in the development of several major regulatory initiatives.

CADTH in 2018: Crossroads, Inflection Points, and Partnerships

Heather Logan, Vice-President, Pharmaceutical Reviews (Acting), Canadian Agency for Drugs and Technologies in Health (CADTH)

[Abstract not available]

Heather Logan
Heather Logan is CADTH's Vice-President, Pharmaceutical Reviews (Acting), with responsibility for the CADTH Common Drug Review, the pan-Canadian Oncology Drug Review, therapeutic class reviews, and optimal use projects, as well as drug-related Environmental Scans, Horizon Scans, and Rapid Response. Heather and her team deliver high-quality, relevant, and timely assessments of drugs using the best available science, tools, and methodologies.

With more than 20 years of experience working with local, provincial, national decision-makers, she is known for her facilitative leadership style and for being results-driven. With a background as a Nursing Officer in the Canadian Armed Forces, a health care administrator, and a systems leader, she brings a unique and collaborative perspective.
Heather is married with two children. She has a Bachelor of Science in Nursing and a Masters of Health Science from the University of Toronto.

PMPRB Framework Modernization

Douglas Clark, Executive Director of Patented Medicine Prices Review Board

Patented drug prices in Canada are among the highest in the world and per capita spending on prescription drugs is second only to the United States. In addition, an influx in very high cost drugs is driving growth in pharmaceutical spending at alarming rates. Over the past decade, the average annual cost of the top ten selling drugs in Canada increased by over 1500% and the number of drugs with annual per-patient treatment costs of at least $10,000 leapt from 20 to 135. Fully 25% of public and private insurer spending is allocated to these drugs, which cover only 1% of beneficiaries.

Excessive pharmaceutical spending can limit access to innovative drugs by straining the budget envelope of public and private insurers, place a financial burden on those who pay out of pocket for their medicines, and mean fewer resources for other critical areas of the health care system. As part of the federal government's commitment to improve the affordability of prescription drugs in Canada, it is advancing major reforms to the Patented Medicine Prices Review Board (PMPRB) a federal regulator that protects consumers from excessively priced patented drugs These reforms would enable the PMPRB to benchmark Canadian prices to a less expensive grouping of OECD member countries and consider value (cost effectiveness) and affordability (market size) when setting ceiling prices for new patented drugs in Canada.

Douglas Clark

Doug has a background in international trade law, intellectual property policy, competition law enforcement and pharmaceutical pricing and reimbursement.

Doug attended McGill University, the University of New Brunswick and l'Université de Moncton. He obtained his law degree in1997 and was called to the Ontario Bar in 1999 after a clerkship with the Federal Court of Appeal.

In 2000, Doug was hired by the federal government to help defend against two WTO challenges to Canada's drug patent regime. In 2006, he became Director of Patent and Trademark Policy at Industry Canada where he was responsible for Canada's Access to Medicines Regime, changes to the Patented Medicines (Notice of Compliance) Regulations and special trademark legislation for the 2010 Vancouver Winter Olympics. In 2009, Doug joined the Competition Bureau as Assistant Deputy Commissioner, Civil Matters, where he led a number of high profile prosecutions under the *Competition Act.*

Doug became Executive Director of the PMPRB in October 2013.

Panel Discussion: Panel Members

Ed Dybka

Ed Dybka is the President of QIV Capital Management working with the biopharmaceutical industry, academia and government. Previously he was President & CEO of AstraZeneca Canada Inc., part of AstraZeneca PLC, one of the world's leading biopharmaceutical companies.

Mr. Dybka has worked in the Canadian pharmaceutical industry for over 30 years. In 2012, he led the Canadian establishment of Almirall Canada Inc., a start-up biopharmaceutical company focused on the treatment of respiratory diseases.

Prior to establishing Almirall in Canada, Mr. Dybka held a number of executive roles at GlaxoSmithKline Canada including Vice President of Marketing, Sales and Public Affairs & Reimbursement. During this time, he was accountable for the marketing and sales of all GSK pharmaceutical products, including specialty care, oncology and vaccines, achieving strong commercial performance and employee engagement. Earlier in his career, Mr. Dybka held progressively senior roles in product management and product development, as well as sales, at Glaxo Wellcome Canada Inc. and Zeneca Pharma Inc.

Mr. Dybka is currently Co-Chair of Life Sciences Ontario, a Director of Clinical Trials Ontario and he is also the Chair of the Acute Coronary Treatment (ACT) Foundation. He is a current member of the Life Science Working Group advising the Ministry of Research & Innovation for the Province of Ontario on it's Life Sciences Economic Strategy. He is also a member of the Health/Biosciences Economic Strategy Table for the Federal Ministry of Health and Ministry of Innovation, Science and Economic Development.

He has served on a number of other Boards including Innovative Medicines Canada, the Pharmaceutical Advertising and Advisory Board, the Canadian Pharmaceutical Distribution Network, The Mississauga Board of Trade and The George Hull Centre for Children and Family.

Durhane Wong-Rieger

Durhane Wong-Rieger, PHD, is President & CEO of the Canadian Organization for Rare Disorders (the umbrella organization of patients and patient groups) and chair of the Consumer Advocare Network (a national network for patient engagement in healthcare policy and advocacy). She is also President & CEO of the Institute for Optimizing Health Outcomes (providing training and direct service on health coaching and patient self-management) and Chair of the Canadian Heart Patient Network. Internationally, Durhane is Chair of Rare Disease International (the global alliance of rare disease patient organizations), Past-Chair of the International Alliance of Patient Organizations, member of the Editorial Board of *The Patient-Patient Centred Outcomes Research,* member of the *Global Commission to End the Diagnosis Odyssey for Rare Diseases* and member of Health Technology Assessment International Patient /Citizen Involvement Interest Group. She is a certified Health Coach and licensed T-Trainer with the Stanford-based *Living A Healthy Life with Chronic Conditions*.

Dr. Wong-Rieger has served on numerous health policy advisory committees and panels and is a member of the Ontario's Rare Disease Implementation Working Group, member of Genome Canada Steering Committee for the Rare Disease Precision Health Initiative and member of the Patient Liaison Forum for the Canadian Drugs and Technologies in Health.

Durhane has a PhD in psychology from McGill University and was professor at the University of Windsor, Canada from 1984-1999. She is married and has two children. She is a trainer and frequent lecturer and author of three books and many articles.

Wednesday, May 23

SESSION 1C:

Crossing Biological Membranes

Co-Chairs: Emmanuel Ho, University of Waterloo, and Kerry Goralski, Dalhousie University

Improving Predictions of Renal Anionic Drug Transport

Ryan M. Pelis, PhD, Associate Professor, Department of Pharmacology, Dalhousie University

The kidney is important for eliminating from the body a structurally diverse array of small molecular weight drugs that carry a net negative charge at physiological pH, i.e., anionic drugs. The renal elimination of anionic drugs is accomplished in part by tubular secretion mediated by organic anion transporters. My laboratory is focused on using *in vitro* transport kinetic data and physiologically-based pharmacokinetic (PBPK) modeling to predict the involvement of renal organic anion transporters in drug disposition and drug-drug interactions. One major hurdle in generating accurate PK predictions with PBPK modeling is the generation of physiologically-relevant transport kinetic constants *in vitro*. Much of our recent work has focused on studying ligand interactions with the organic anion transporter 1 (OAT1), an anionic drug uptake transporter expressed at the basolateral membrane of renal proximal tubule cells. Here I will discuss our recent studies that aim to find the most physiologically-relevant condition *in vitro* for accurate PK predictions with OAT1 by PBPK modeling. The first kinetic studies that I will describe are those conducted under 'zero-*trans*' (i.e., 'sink') conditions, where upon initiation of transport the concentration of substrate inside of the cells is zero. Saturation kinetic studies were performed at various time-points, from initial-rate to steady-state, to examine the influence of time on the kinetic constants, maximal transport rate (J_{max}) and Michaelis constant (K_m). We also performed inhibition studies at various incubation times under zero-*trans* conditions to determine the effect of time on inhibition potency (IC_{50} determination). The second set of studies that will be described are those conducted under 'equilibrium exchange' conditions, where drug is allowed to fully equilibrate across the plasma membrane prior to performing saturation kinetic studies. The kinetic constants from the zero-*trans* and equilibrium exchange experiments were then input into the Mechanistic Kidney model within the Simcyp Simulator for PK predictions. Our data show that there is a significant effect of time on J_{max}, K_m and IC_{50} values, and that the time chosen profoundly influences PK and DDI predictions at OAT1 by PBPK modeling.

Ryan M. Pelis

The Pelis laboratory studies drug transport energetics and how it influences tissue drug concentration-time profiles – i.e., pharmacokinetics. His major research focus is on using in vitro drug transporter kinetics and physiologically-based pharmacokinetic (PBPK) modeling to predict drug concentration-time profiles. With in vitro data and PBPK modeling we are moving toward predicting interindividual variability in drug exposure and response due to factors such as disease, genetics and drug-drug interactions. This information is essential for the clinical registration of investigational drugs with the major pharmaceutical regulatory agencies (FDA & EMA). With this information we will help make more cost-effective and safer pharmaceutical therapies for individualized medicine.

Dr. Pelis graduated from the University of Massachusetts with a Bachelor of Science in Animal Science and a Master of Science in Biology. He received his Ph.D. in Physiology and Neurobiology from the University of Connecticut and completed his Postdoctoral Fellowship in the Department of Physiology at the University of Arizona. Much of his training was spent with the US Geological Survey (Turners Falls, MA) and the Mount Desert Island Biological Laboratory (Bar Harbor, ME). From 2009-2012 Ryan was a Senior Investigator and Laboratory Head in the Drug-Drug Interactions Section in the Department of Drug Metabolism and Pharmacokinetics at the Novartis Institutes for Biomedical Research in East Hanover, NJ. At

Novartis he managed an in vitro drug metabolism and drug transport laboratory whose purpose was to support Investigational New Drug Applications (INDs) and New Drug Applications (NDAs). From 2012-2018 he was an Assistant and then an Associate Professor in the Department of Pharmacology in the Faculty of Medicine at Dalhousie University in Halifax, NS, Canada. He recently joined the Department of Pharmaceutical Sciences in the newly-established Pharmacy program at the State University of New York in Binghamton, NY.

I am looking for students and postdocs, so please come see me!

Disruption of Model Membranes by Surfactants used in Gene Delivery

Shawn Wettig, Ph.D., C.Chem., Associate Professor and Associate Director, Graduate Studies and Research, School of Pharmacy, University of Waterloo, Waterloo, ON

Gene delivery relies on the delivery of a specific gene of interest to target cells. One of the major barriers to successful gene therapy is the transport of the DNA across cellular membranes into the cell. Synthetic gene therapy vectors rely on the use of various cationic agents (polymer, lipid, or surfactant) to condense and package DNA, and to facilitate its transport across cellular membranes. In this talk I will discuss studies of lipid monolayers (used as a simplistic model for a cellular membrane) which were treated with a nanoparticle based gene therapy. Langmuir isotherms were obtained for each system, along with images obtained using Brewster Angle Microscopy. The results are interpreted based upon the effect that the components of the nanoparticle formulation has on the compressibility of the model membrane systems.

Shawn Wettig

Dr. Wettig obtained his Ph.D. studying the physical chemistry of novel mixed surfactant/polymer systems with Dr. Ron Verrall in the Department of Chemistry at the University of Saskatchewan. His research interests lie in the general areas of biophysical chemistry and nanotechnology; in particular at the interface of these two broadly defined areas. This research involves aspects of physical chemistry, solution thermodynamics, biochemistry and cell biology applied to the study of self-assembling systems. While self-assembly is a readily recognized tool in the design of systems for drug delivery applications, the use of self-assembly in the so-called "bottom-up" construction of nano-particulate systems for drug delivery applications is an emerging field. A key aspect of this research is the design of novel surface-active compounds (surfactants) that, in addition to providing the desired characteristics of self-assembly and control of particle dimensions on the nanometer size scale, can also provide enhanced pharmaceutical applications such as targeted delivery and/or enhanced bio-distribution of an active compound. For more details on his research program see Dr. Wettig's research website at uwaterloo.ca/wettig-research-group/.

Medicating the Brain: The Challenges of Getting Drugs Past the Blood-Brain Barrier

Donald W. Miller, Department of Pharmacology and Therapeutics, University of Manitoba

The brain microvessel endothelial cells that form the blood-brain barrier (BBB) have an important role in maintaining the proper extracellular environment for central nervous system (CNS) function. This same cellular barrier also presents a formidable obstacle to the delivery of many drugs to the brain. The expression of a wide variety of transporter systems that allow for selected transcellular passage through the BBB and the presence of complex tight junctions that limit paracellular diffusion across the BBB encompass the two most prominent features that distinguishes the brain microvasculature from microvasculature in peripheral tissues. They also represent the two extremes of efforts to enhance drug penetration across the BBB. With over 200 different solute carriers (SLCs) and 38 different ATP-binding cassette (ABC) proteins expressed in human brain microvessel endothelial cells, there is a diverse array of uptake and efflux systems for moving selected drugs into and out of the brain. In this regard, much emphasis has been placed on the importance of drug efflux transporters, such as P-glycoprotein, in the BBB. From a paracellular diffusion standpoint, there is growing interest in capitalizing on transient changes in tight junction complexes within the brain endothelial cells that provide therapeutic windows for enhanced drug delivery to the brain. Studies highlighting both transporter-based and paracellular approaches to

CNS delivery and the challenges inherent in each approach will be discussed.

Donald Miller
Dr. Miller received his PhD in Pharmacology and Toxicology from the University of Kansas. After completing a postdoctoral fellowship in the laboratory of Dr. Ronald Borchardt in the Department of Pharmaceutical Chemistry at the University of Kansas, he accepted a position as Assistant Professor in the Department of Pharmaceutical Sciences at the University of Nebraska Medical Center. In 2006 he was recruited to the Department of Pharmacology and Therapeutics at the University of Manitoba where he is currently a Professor and Principal Investigator in the Kleysen Institute for Advanced Medicine. Dr. Miller's research focus is on understanding the cellular signalling pathways influencing blood-brain barrier (BBB) permeability under normal and pathological conditions and on the development of approaches for enhancing drug delivery to the brain. Using both cell culture and animal models, Dr. Miller has mechanistically examined drug efflux transporters and their impact on BBB permeability. In addition to transcellular routes of drug penetration in the BBB, his laboratory is also examining methods for transiently modulating the paracellular pathways for delivery of drugs and nanomaterials to the brain with a primary focus on improved treatment of brain tumors. He has participated on grant review panels for CIHR, NIH, European Union, and Austrian Science Federation, and is currently a member of the scientific advisory board for Vireo Systems LLC (Nashville, TN).

Optimizing Nanoparticle Interactions with Macrophages and Endothelial Cells

Joy Wolfram, PhD, Assistant Professor, Department of Transplantation and Department of Physiology and Bioengineering, Mayo Clinic, Jacksonville, Florida, United States

The ultimate goal of drug delivery is to direct and confine therapeutic agents to specific locations in the body in order to reduce side effects and increase therapeutic efficacy. Site-specific delivery necessitates implementation of nanoparticle design and microenvironmental modification strategies to achieve favorable interactions with biological membranes. In particular, the shape and size of nanoparticles can be optimized to increase binding to tumor endothelial cells through exploitation of hemodynamics. Nanoparticles display increased interactions with the vessel wall due to tumor blood flow characteristics, resulting in enhanced exposure of cancer cells to therapeutic agents. Specifically, large discoidal nanoparticles display preferential binding to cancer vasculature. Additionally, the microenvironment of the mononuclear phagocyte system can be altered with pharmacological agents to reduce nanoparticle clearance by macrophages. Notably, systemically injected nanoparticles accumulate preferentially in tissue-resident macrophages of the liver and spleen, thereby limiting site-specific delivery. In fact, drug-repurposing strategies, such as the use of chloroquine, are promising for modulating macrophage activity to obtain reduced nanoparticle endocytosis. The encouraging preclinical results of the abovementioned nanoparticle design and microenvironmental preconditioning strategies will be discussed, as well as ongoing strategies for clinical translation. In conclusion, optimization of nanoparticle interactions with biological membranes is promising for improving the treatment of disease.

Joy Wolfram, PhD
Dr. Joy Wolfram is an Assistant Professor of Medicine at the Mayo Clinic in Florida, where she leads the Nanomedicine and Extracellular Vesicles group. She also holds affiliate faculty positions in the Department of Nanomedicine at the Houston Methodist Hospital in Texas, the Department of Biology at the University of North Florida in Florida, and the Wenzhou Institute of Biomaterials and Engineering at the Ningbo Institute of Industrial Technology in China. She received her bachelor's and master's degrees in biology from the University of Helsinki in Finland. In 2016, she completed her Ph.D. in nanoscience and technology at the University of Chinese Academy of Sciences in China. In the past five years, she has authored over 40 publications and received more than 25 scientific awards from seven different countries. She was included in the Amgen Scholars Ten to Watch List, which highlights the best and brightest up-and-comers in science and medicine across 42 countries. She has developed several nanoparticles for the treatment of various diseases, including cancer. Her goal is to bring new nanomedicines with increased therapeutic efficacy and safety to the clinic. Her mission is also to inspire and support underrepresented minorities in science. She is actively involved in community outreach and scientific education.

Wednesday, May 23

CSPS Lifetime Achievement Award Lecture

Gordon Amidon, University of Michigan

Chair: Fakhreddin Jamali, University of Alberta

Don't Throw the BA/BE out with the Bathwater (Mechanistic Oral BE)

Gordon L. Amidon Ph.D**.,** William I. Higuchi Distinguished University Professor of Pharmaceutical Sciences; Charles R. Walgreen Jr. Professor of Pharmacy and Pharmaceutical Sciences; University of Michigan, College of Pharmacy; Department of Pharmaceutical Sciences, Ann Arbor, Michigan

Bioequivalence (BE) is usually taught as a relative Bioavailability (BA) science…which it unquestionably is! However, the fact that BE is a test of product differences with the same drug (API) is often overlooked. This implies that the 'A' part of ADME is responsible for the differences in *in vivo* BE, since the 'DME' of the two products is the same, with some exceptions. Consequently, for most drug products it is the interaction of the drug product with the absorbing site where the difference in drug product *in vivo* performance occurs.

This mechanistic approach to oral product performance and bioequivalence, which led to the widely accepted Biopharmaceutics Classification System (BCS) will be further elaborated in this seminar through recent studies simultaneously measuring gastrointestinal events and oral plasma levels. These *in vivo* studies, in normal subjects, have revealed the very low buffer capacity of the gastrointestinal tract and a very significant effect (correlation) of gastrointestinal motility on oral drug plasma levels. These results imply that much of the variability in oral drug product plasma levels is due to gastrointestinal variation, since we dose subjects randomly relative to this GI variation. Our recent results imply that we need to update and revise our FDA and USP product regulatory standards to ensure continued product efficacy.

Gordon L. Amidon

Dr. Gordon L. Amidon received his B.S. degree from the State University of New York, Buffalo (1967), an M.A. degree in Mathematics (1970) and Ph.D. in Pharmaceutical Chemistry (1971) from The University of Michigan. From 1971 to 1981 Dr. Amidon was a member of the faculty at the University of Wisconsin. He was appointed Professor of Pharmaceutics at The University of Michigan in 1983 and was named the Charles R. Walgreen, Jr., Professor of Pharmacy in 1994. Dr. Amidon is internationally known for his research in the field of drug absorption, transport phenomena, solubility, dissolution, and prodrugs. He has published 375 papers and 370 abstracts, and has18 US patents. Professor Amidon has mentored more than 120 doctoral and postdoctoral students with over 20 selecting academic careers. Dr. Amidon has received numerous awards, including, in September of 2017, the William I. Higuchi Distinguished University Professor of Pharmaceutical Sciences at the University of Michigan. Dr. Amidon developed a Biopharmaceutics Classification System (BCS), with the FDA, impacting bioequivalence standards worldwide. He currently continues his dissolution work with the FDA, with current contract funding.

Wednesday, May 23

SESSION 2A:

Knowledge Translation - From Real World Evidence to Canadian Health Care Needs

Chair: George Wells, University of Ottawa, and University of Ottawa Heart Institute

Session Chair:

George A. Wells, MSc, PhD, University of Ottawa, and Cardiovascular Research Methods Centre, University of Ottawa Heart Institute

Dr. Wells is a Professor in the School of Epidemiology, Public Health at the University of Ottawa and Director of the Cardiovascular Research Methods Centre at the University of Ottawa Heart Institute. He is also a Professor in the Department of Medicine and a Senior Investigator at the Ottawa Hospital Research Institute at the Ottawa Hospital.

His research interests are in the design and analysis of clinical trials, statistical methodology related to health care delivery, systematic reviews and meta-analysis, economic evaluations and the development and assessment of decision support technologies for patients and practitioners. Dr. Wells is the author or co-author of over 800 published articles and 900 scientific abstracts. He has been the principal investigator or co-investigator on over 270 research projects. He has taught at the University graduate and undergraduate level for 36 years and has supervised over 90 graduate students.

Dr. Wells has worked extensively with national and international government and non-government research organizations, as well as private pharmaceutical and biotechnology industries. He has been on the executive and steering committees of national and international research programs, external safety and efficacy monitoring committees, scientific grant review committees, editorial committees and, scientific advisory committees. He is currently an Associate Editor of the Journal of Clinical Epidemiology and on the Editorial Committee of the Canadian Medical Association Journal.

Public Payer Perceptions of the Value of Real World Evidence

Don Husereau, University of Ottawa, School of Epidemiology and Public Health

Canada has a long history of the use of research evidence to support healthcare decision-making. Although there have been recent improvements in data holdings and analytic capacity in Canada, there remain questions about the perceptions of the value of real-world evidence in reimbursement and decision-making barriers to its optimal use in pricing and reimbursement, current initiatives that may lead to its increased use, and what role the pharmaceutical industry may play in this. Methods: To capture stakeholder perceptions, 91 participants identified as key stakeholders were identified according to background roles and geography and invited to participate in four round table discussions conducted under Chatham House rule. Important themes emerging from these discussions included: 1) The need to understand what "real world" evidence means; 2) Barriers to using real world evidence from differences in access, governance, inter-operability, system structures, expertise and quality across Canadian health systems; 3) Differing views on industry's role. Conclusions: The use of real-world data in Canada to inform pricing and reimbursement decisions is far from routine but nascent and slowly increasing. The federated structure of Canada’s health system and the lack of universal public insurance for drugs have led to initiatives that have been focused on the networking of healthcare administrative data acrossprovincial jurisdictional boundaries. There also appears to be a desire to see better use of pragmatic trials linked to these administrative data sets. Emerging initiatives have been funded to use real world evidence more broadly.

Don Husereau
Don Husereau is the Senior Economic Advisor to the CPhA. He is an Adjunct Professor of Medicine at The University of Ottawa and Senior Associate with the Institute of Health Economics. He has expertise in health technology and policy assessment, and was a former Director and Senior Advisor for the Canadian Agency for Drugs and Technologies in Health. Don is currently Chair of an International Task Force that has developed consolidated health economic evaluation reporting standards (CHEERS) that is now endorsed by leading biomedical and health policy journals. Don is currently an Editorial Advisor for the biomedical journals, Value in Health and BMC Medicine. He is also Senior Scientist at the University for Health Sciences, Medical Informatics and Technology in Hall in Tirol, Austria. Most recently, Don served on the pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) and currently serves on the Ontario Committee to Evaluate Drugs. Don received both his BSc and MSc from the University of Alberta's faculty of Pharmacy and Pharmaceutical Sciences.

Improving the Use of Real World Evidence in the Regulatory Environment: Where Are We Heading?

Rhonda Kropp, Director General, Marketed Health Products Directorate, Health Products and Food Branch, Health Canada

Health Canada has recently launched an initiative to improve the regulatory review of drugs and devices with an eye towards making the system more efficient, supporting more timely access to therapeutic products and building better linkages within the healthcare system as a whole. As part of this initiative, Health Canada is working in collaboration with its key partners to improve how it can access and analyze Real World Data (RWD) with the objective of optimizing decision-making across the life cycle of health products. This project, called *"Enhancing the Use of Real-World Evidence (RWE) Throughout the Life Cycle of Health Products"*, will explore the key information gaps impacting our ability to monitor performance of marketed health products across their life cycle, and the role RWE can play in filling those gaps. We are also assessing the existing use of RWE to better understand how we can optimize its use throughout the product life cycle. The project is expected to result in enhanced monitoring of the performance of health products in Canada, which will contribute to improved access to health products, especially those products and for populations for which assessment through randomized clinical trials is less feasible. This work will also improve our ability to share information on health product safety and effectiveness which is important for the decision making of health care providers, patients and others in the health care system. This presentation will outline the plans and provide a status update for this work.

Rhonda Kropp
Rhonda Kropp is currently the Director General for the Marketed Health Products Directorate in the Health Products and Food Branch of Health Canada. She is responsible for the oversight of the vigilance of marketed health products in Canada, including ensuring Canadians and health professionals are informed of important issues impacting the safety and effectiveness of health products in a timely fashion.

Rhonda has been working in health policy, programs and surveillance for over 20 years as a nurse, microbiologist, researcher and infectious disease epidemiologist. She started her career as a microbiologist in an industry laboratory. After returning to school to get her degree in Nursing, she worked as a paediatric oncology nurse at British Columbia Children's Hospital before pursuing graduate school in public health at the University of California, Berkeley. After a few years directing public health research projects in California for the state government, Stanford University and the University of California, San Francisco, Rhonda joined the Government of Canada through the Recruitment of Policy Leaders program in 2003.
During her fourteen years with the Government of Canada, Rhonda has taken on a diversity of roles from technical expert and epidemiologist to policy manager before joining the Executive cadre. Within her last five years in the federal public service, she served as the Chief Health Surveillance Officer and the Director General of the federal immunization program at the Public Health Agency of Canada before joining Health Canada in December 2017. Rhonda was the proud recipient of the Chief Public Health Officer of Canada medal in 2017 for outstanding performance.

Canadian Network for Observational Drug Effect Studies: Using Real-World Evidence to Inform Regulatory Decisions

Robert Platt, McGill University Health Centre Research Institute, Montreal, QC

The Canadian Network for Observational Drug Effect Studies (CNODES) was formed in 2011 as a component of the Drug Safety and Effectiveness Network, a collaborative venture between CIHR, Health Canada, and other stakeholders. CNODES addresses queries from Health Canada and other groups on drug utilization, safety, and effectiveness, using administrative data-based cohorts from most Canadian provinces, the US, and the UK. CNODES' work has addressed safety concerns associated with several frequently-used medications including statins, proton-pump inhibitors, antipsychotic medications, and anti-acne medications. CNODES has had significant impact on regulatory policy. CNODES develops protocols in close collaboration with query submitters, and involves decision-makers at several points in the query development and research process. Recently CNODES researchers have implemented a common data model across the Canadian databases, which will enable rapid-response analyses for straightforward queries using semi-automated computer programs, and faster turn-around for decision-makers. I will describe CNODES processes and interactions with Health Canada and other stakeholders, and provide several examples of CNODES' work.

Robert Platt

Robert Platt is Professor in the departments of Pediatrics in addition to Epidemiology, Biostatistics, and Occupational Health (EBOH) at McGill University, and Director of Graduate Programs in the department of EBOH. He holds the Albert Boehringer I endowed chair in Pharmacoepidemiology.

Dr. Platt is the Executive Co-Lead of the Canadian Network for Observational Drug Effect Studies (CNODES). He has been the leader of the Methods team of CNODES since its inception. In this role, he has led a methods research and training program for the network and has participated as methods liaison (senior methods author) in numerous CNODES studies.

After completing his PhD in Biostatistics at the University of Washington in 1996, he joined the faculty at McGill University. His main research interests are statistical methods and applications for administrative data, pharmacoepidemiology, perinatal epidemiology, and methods for causal inference from epidemiological studies. His methodological interests center on marginal structural models for analyses of large administrative data cohorts, in particular the specification and optimization of the propensity score and inverse probability weights.

Dr. Platt is principal investigator on a number of grants, including a Foundation Grant from the Canadian Institutes of Health Research (CIHR) and a Discovery Grant from the Natural Sciences and Engineering Council of Canada. He is co-investigator/subcontractor on several other CIHR and National Institutes of Health grants. In 2005, Dr. Platt received the *Prix d'Excellence* from the Québec Foundation for Research on Children's Diseases. Dr. Platt is a 2016 Thomson Reuters Highly-Cited Researcher.

Dr. Platt is on the editorial board of the American Journal of Epidemiology, Pharmacoepidemiology and Drug Safety and Current Epidemiology Reports, and is Associate Editor of Statistics in Medicine and the International Journal of Biostatistics. He has published over 300 articles, one book and several book chapters on epidemiology.

Life-Cycle HTA: Unlocking the Potential for Real World Evidence

Tammy Clifford, Chief Scientist & Vice President, Evidence Standards, CADTH

Traditionally, CADTH and other Health Technology Assessment (HTA) organizations have focused their assessments on new drugs and other health technologies, at the point of their adoption into the health care system. These decisions are often binary in nature (e.g., adopt or not, fund or not) and are often made with considerable uncertainty. Quality and efficiency are not simply a function of whether a technology is available; it is equally important to manage how, how often and how well the technology is used in the real world.

With the launch of its new strategic plan, CADTH aims to support the transformation of how our system manages health technologies. Integral to this shift from health technology assessment (HTA) to health technology management (HTM) is a move

away from one-time decisions, made at the time of a technology's adoption, to supporting decisions at all phases of the technology life-cycle, from pre-market to adoption, to actual use in real-world setting, through to disinvestment and decommissioning. In order for HTM to be a success, we need greatly expanded and continuous evaluative capacity to ensure the health care system effectively manages the entry, ongoing use, and exit of technologies.

Many decisions about health technologies are made with considerable uncertainty at product launch. CADTH will establish guidelines and processes for the reassessment of drugs, devices and interventions already in use within the system. This will allow for new recommendations to be made, facilitate adjustments to both pricing and practice guidelines, and promote disinvestment in technologies that provide low value to Canadians (thereby enabling re-investment elsewhere). To be effective, this will require coherent mechanisms for identifying technologies amenable to reassessment and will rely, in part, on the use of RWE.

This session will provide insights into CADTH's new strategic plan, highlighting opportunities for collaboration with others in the RWE space so as to enable the effective management of health technologies within a living healthcare system.

Tammy Clifford

Dr. Tammy Clifford is CADTH's Chief Scientist and Vice President, Evidence Standards. Over the past decade, she has served in a number of senior leadership roles at CADTH, with responsibility for the agency's Health Technology Assessment (HTA), Horizon Scanning, Rapid Response, Scientific Advice and Patient Engagement programs. Tammy received her PhD in Epidemiology & Biostatistics at the University of Western Ontario, and her BSc and MSc from McGill. Through her role as an adjunct professor with the School of Epidemiology, Public Health & Preventive Medicine at the University of Ottawa, Tammy is building awareness of and capacity in HTA through her active involvement with the graduate program where she both teaches and supervises MSc and PhD students. She has been actively involved with national and international HTA activities, including having served on the Board of Directors of Health Technology Assessment international (HTAi), the international society for the promotion of HTA, and having participated in the development of the scientific programmes for many HTAi annual meetings. Tammy is internationally recognized for her passion and commitment to advancing the science of HTA, and to mentoring the next generation of HTA producers

Wednesday, May 23

SESSION 2B:

Pharmaceutical Potential of Stem Cell & CRISPR-mediated Gene Modifications

Chair: Jeffrey Henderson, University of Toronto

Stem Cell Activation to Promote Self-Repair of the Injured Nervous System

Cindi M Morshead, PhD, Professor and Chair, Anatomy, Department of Surgery, Donnelly Centre, University of Toronto, Toronto, ON

The discovery of neural stem cells has led to significant interest in their use for neural repair. We are interested in developing therapeutic interventions that can harness the potential of resident neural stem cells and their progeny (together termed neural precursor cells, NPCs) to promote tissue repair and functional recovery. Herein, I will focus on our work using the drug Metformin, a drug typically used to treat type II diabetes, which we have shown to expand the size of the NPC pool and promote neurogenesis and oligogenesis. Moroever, the administration of Metformin promotes motor recovery in a model of neonatal stroke. Chronic administration of metformin also leads to a rescue of cognitive deficits in this same model, but this only occurs in females, and not males. I will discuss our recent work investigating how the factors of age, sex and brain region modulate the response of NPCs to metformin in the intact and injured brain. Our findings indicate that the stem cell niche plays an important role in regulating the NPC response to metformin, which has important implications for the development of therapeutics to treat the injured brain.

Cindi Morshead

Dr. Morshead did her PhD at the University of Toronto and joined the Department of Surgery in 2003. She is currently a tenured Professor and Chair of the Division of Anatomy, Department of Surgery. Dr. Morshead's expertise is in stem cell biology and specifically, in the field of adult neural stem cells. Her lab is interested in exploring fundamental questions regarding the behaviour and characterization of neural stem cells and applying this knowledge to regenerative medicine strategies. Her team is actively pursuing the role of endogenous stem cells in models of neurodegenerative disease such as stroke, cerebral palsy, acquired brain injury and spinal cord injury.

A Stemness-based Drug Screen to Target Acute Myeloid Leukemia Stem Cells

Jean Wang MD PhD, Princess Margaret Cancer Centre, University Health Network

Acute myeloid leukemia (AML) is an aggressive hematologic malignancy with poor prognosis, especially for older patients. Although conventional intensive chemotherapy reduces bulk disease and induces morphologic remissions in most patients, the disease frequently recurs due to the persistence of leukemia stem cells (LSCs), which possess stem cell properties such as self-renewal and quiescence that are linked to therapy resistance and relapse. Novel therapies that eradicate L SCs through disruption of pathways required for stemness have the potential to produce durable responses and improve clinical outcomes. Previous drug discovery approaches in leukemia have been largely unsuccessful, in no small part due to the use of established AML cells lines that do not retain the functional hierarchy of primary AML clones, and the use of surrogate endpoints such as bulk cell viability or proliferation that poorly reflect drug activity against LSCs. Thus, many drugs that move forward from such screens ultimately fail to improve patient outcomes in clinical trials. The best functional assay for studying LSC properties is xenotransplantation of patient samples into immunocompromised mice. However, labour-intensive xenotransplantation assays are impractical to perform on a large scale and are prohibitively

costly for drug discovery studies. To address these issues, we have developed a next-generation high-throughput drug discovery approach designed to identify novel compounds with activity against LSCs, using a functionally-validated LSC-specific gene signature that captures the core transcriptional programs associated with stemness.

Jean Wang
Jean Wang is a Clinician Scientist and Staff Hematologist at the University Health Network in Toronto, and an Affiliate Scientist at Princess Margaret Cancer Centre. Her research currently focuses on acute myeloid leukemia (AML), one of the most deadly types of leukemia and the most common type of acute leukemia in adults. Through the use of xenotransplantation models of AML, Dr. Wang studies the biology of the leukemia stem cells (LSC) that underlie therapy resistance and relapse, and evaluates the efficacy of novel anti-leukemia agents against LSCs, with parallel development of drug response biomarkers for patient stratification in clinical trials. Her group recently developed a robust LSC gene signature for rapid determination of risk in newly-diagnosed AML patients, and she is currently working with colleagues at Princess Margaret to bring her research findings to the clinic.

Opening the Gate for Pluripotent Stem Cell-based Therapies

Andras Nagy, Lunenfeld-Tanenbaum Research Institute, Sinai Health System, Toronto, Canada

Pluripotent stem cells have accelerated the development of new avenues for targeting degenerative diseases and cancer with cell-based therapies. Numerous human therapies are currently on their way to treat devastating conditions. However, concerns about the cell-safety hold back the full utilisation of these promising new treatments. Here we introduce a concept and show the associated genome engineering strategy that addresses this issue and provides a solution for "fail-safe" cell therapies.

To ensure the reliable expression of a suicide transgene system in proliferating cells, we transcriptionally linked it to a cell division essential endogenous locus (CDEL) in a homozygous manner. Our prototype suicide gene was the herpes simplex virus-thymidine kinase (HSV-TK), and the prototype CDEL was CDK1. The coding regions of these two kinases were connected with a viral 2A sequence. Using mouse and human embryonic stem cell lines with the above homozygous modification, we showed an extremely efficient and reliable ablation of proliferating cells both *in vitro* and *in vivo* by ganciclovir treatment, the pro-drug for HSV-TK.

Using published and our experimental measures of forward mutation rates, we defined mathematically the level of safety of therapeutic batches of these cells. Our general approach to assess and quantify the safety will be critical to make informed decisions by the regulators, doctors, and patients to advance the modern medicine-transforming cell therapies.

Building on the fail-safe technology, we addressed the next hurdle faced by cell therapies; a solution for induced allograft tolerance. We showed that the expression of eight local-acting, immunomodulatory transgenes introduced into embryonic stem cells is sufficient to protect cell derivatives against rejection in allogenic, immune-competent recipients. Allografts survive long-term, in different MHC-mismatched recipients, and without immunosuppressive drugs. Most importantly, the recipients of these engineered cells do not have suppressed systemic immune function.

The combination of the fail-safe and immune tolerance genome editing makes the One4All cell line and therapeutic cell development a reality.

Andras Nagy
Dr. Nagy is currently a Shawn Kimel Senior Scientist at the Lunenfeld-Tanenbaum Research Institute, Sinai Health System, Professor in the Department of Obstetrics & Gynaecology and Institute of Medical Science at the University of Toronto, Investigator at the McEwen Centre for Regenerative Medicine and Professor at the Australian Regenerative Medicine Institute in Monash University, Melbourne. He holds a Tier I Canada Research Chair in Stem Cells and Regeneration. He also has a Fellowship of the Royal Society of Canada in the Life Sciences Division of the Academy of Science and recently became a Foreign Member of the Hungarian Academy of Sciences. Dr. Nagy has made significant breakthroughs in the development of mouse and human pluripotent stem cells (both embryonic and induced) that could accelerate research in regenerative medicine and lead to future therapies for currently incurable diseases, such as blindness, diabetes, arthritis, spinal cord injury and

many others. His team created the first two Canadian human embryonic stem cell lines and developed a novel method for generating non-viral induced pluripotent stem cells. His current research focuses on understanding the process of reprogramming to stem cells at the molecular level and using sophisticated genome editing methodology to pave the way leading to safe and effective cell based therapies of diseases.

Network Analysis of Cell Death Signaling Pathways via CRISPR-mediated Modification in Embryonic Stem Cells and Derivatives

Jeffrey Henderson, Faculty of Pharmacy, University of Toronto, Toronto, Ontario

Programmed cell death (PCD) plays a critical role in the proper development and homeostasis of a number of cellular systems in mammals. As such, aberrant execution of PCD has been shown to play a role in a number of human pathologies ranging from cancer to autoimmune disease to neurodegeneration. Modulation of PCD signaling is therefore of key interest to a number of clinical and biomedical applications. Analysis of complex PCD signaling interactions in mammalian cells and tissues has traditionally been hampered both by the kinetic limitations of small molecule and sh/siRNA approaches, and the difficulty in generating genetically comparable sets of null/conditional mutations encompassing the systems of interest. However recent advances in gene modification technologies have vastly altered the general applicability of network approaches toward the analysis of cell signaling systems. Using a Crispr-mediated gene targeting approach in embryonic stem (ES) cells, we have presently developed multiple individually validated guides toward a number of key members of the apoptotic, necroptotic and macro-autophagic PCD signaling networks. Using clonally related Crispr-targeted cell lines in conjunction with *in vitro* cellular differentiation and cellular transplantation *in vivo,* we have examined the role of apoptotic-necroptotic signaling for several forms of cell death. The presence of such cell lineages allows for the rapid profiling of a number of different toxicologic agents with respect to cell death mechanisms. Our studies demonstrate that despite expression of key PCD regulators the influence and regulation of apoptotic/necroptotic signaling can vary markedly as a function of both cellular context, with competitive, cooperative and antagonistic signaling models observed *in vitro* and *in vivo.* We have further validated these findings using pharmacologic approaches in wild-type animals, adding a new layer of complexity to caspase-8/RIP-1 signaling.

Jeffrey Henderson

Dr. Henderson received his doctorate in Physical Biochemistry at the University of Illinois. Following post-doctoral work in molecular neuroscience and transgenics he joined the Faculty of the Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital where his laboratory examined mechanisms of regulated cell death and axon guidance relevant to CNS injury. In conjunction with Drs. R. Hakem and T. Mak he provided the first demonstration of the *in vivo* role of caspase-9 in the CNS; as well as EphB2, ShcB and ShcC with the laboratory of Dr. T. Pawson. In 2002 he joined the University of Toronto, Faculty of Pharmacy the where he heads the Murine Imaging and Histology Core Facility and the Antibody-Epitope Recognition Database. He is the designer of NeuroMouse and developed the first 3D surgical atlases of the murine brain and skull for strains 129Sv/IMJ and C57Bl/6J. In conjunction with the laboratory of Dr. M.R. Henkelman he developed the first probabilistic CNS atlases for murine strains 129Sv, C57Bl and CD1 and the expert systems utilized for cross-comparative probabilistic analyses. His current research focuses on three principle themes: Regulation of programmed cell death signaling in the mammalian CNS, EphB-family mediated control of axon guidance and development of small molecule therapeutics modifying PCD signaling. His present studies aim to elucidate PCD signaling in the CNS in response to a variety of cellular stressors using gene-modification methods such as Crispr to identify key identify molecule interactors in mammals. Dr. Henderson currently serves on the Board of Advisors for the Toronto Centre for Phenogenomics Transgenic Core, Executive and Academic committees for the University of Toronto's Collaborative Program in Neuroscience, the Collaborative program in Cardiovascular Sciences and the Centre for Collaborative Drug Research. His work is generously supported by funding from the CIHR, NIH, NSERC and NARSAD. He is a three time awardee of the Rick Hansen Fellowship in spinal cord research.

Selected CSPS Trainee Abstract Oral Presentation

Investigating the Role of the IKKβ Protein Kinase in Vascular Remodeling Events

Francis Lefebvre, Université de Montréal

(See Poster Abstract # 9)

Wednesday, May 23

SESSION 2C:

CSPT Trainee Oral Presentations

Chair: Tuan Trang, University of Calgary

Galen Wright, University of British Columbia

Khaled Adb-Elrahman, Ottawa University

Britt Drögemöller, University of British Columbia

Anish Engineer, Western University

Elizabeth Greco, Western University

Shrinidh Joshi, North Dakota State University

Anette Surmanski, Western University

Markus Gulilat, Western University

Eliza McColl, University of Toronto

Kamelia Mirdamadi, University of Toronto

Tessa Bendyshe-Walton, University of British Columbia

Jay Fang, Western University

Pierre Thibeault, Western University

Yong Jin (James) Lim, Western University

Thursday, May 24

PLENARY SESSION 3

Tak Mak, Princess Margaret Hospital

Chair: Catherine Lau, Janssen Inc.

The Fourth Pillar of Cancer Treatment: It Takes a Village

Tak-Wah Mak, OC, PhD, DSc (Hons), FRSC, FRS, Ontario Cancer Institute, Princess Margaret Hospital, Toronto

Tumorigenesis involves more than oncogene activation or tumor suppressor inactivation, and the cancer cell genome contains many more alterations than can be targeted at once. A key function of the immune system is to prevent incipient tumor cells from establishing but these cells deploy numerous tactics to evade and neutralize the immune responses they provoke. Techniques of immunotherapy have been devised to stimulate specific components of the immune system to increase cancer cell killing (costimulation) and to render tumor cells once more vulnerable to immune attack (checkpoint blockade). About 30% of cancer patients around the world can now benefit from these immunotherapies, including those suffering from non-small cell lung cancer, urothelial cancer, renal cell carcinoma, melanoma, head and neck squamous cell carcinoma, and Hodgkin lymphoma. Ongoing clinical trials are exploring combinations of checkpoint inhibitors, although the enhanced efficacy of this approach produces increased adverse effects. Thus, new avenues beyond checkpoint inhibition are under investigation, including manipulation of the tumor microenvironment. A key goal is to undo the immune-privilege created by the infiltration of regulatory and coopted effector T cells expressing immunosuppressive molecules. Techniques of adoptive T cell transfer (receipt of T cells expanded and activated *ex vivo*) and T cell vaccination may fulfill the promise of personalized medicine, as may CAR-T cell immunotherapy with its T cells expressing engineered anti-tumor receptors. These exciting new frontiers in medical innovation would not have been possible without the cloning of the gene encoding the human T cell receptor (TCR) beta chain. This finding not only solved a problem plaguing scientists for decades but also opened up novel research avenues and provided the basis for new genetic tools used to study how T cells operate and develop, to dissect mechanisms of autoimmunity and tumor cell survival, and to formulate new pathways to cancer eradication.

Tak-Wah Mak

Dr. Tak W. Mak is the Director of the Campbell Family Institute for Breast Cancer Research at the Princess Margaret Cancer Centre in Toronto. He received a bachelor's of science in biochemistry in 1967 and a master of science in biophysics in 1968 from the University of Wisconsin. He earned his Ph.D. in Biochemistry from the University of Alberta in 1971. He is also senior scientist in the division of Stem Cell and Developmental Biology, Ontario Cancer Institute. Since 1984, he has been a Professor in the Departments of Medical Biophysics and Immunology at the University of Toronto.

Dr. Mak co-discovered the t-cell receptor, a key component of the immune system. His research is concentrated on gaining fundamental knowledge of the biology of cells in normal and disease settings, and in particular on the mechanisms underlying immune responses and tumorigenesis. His lab has initiated several complementary programs, many of which have evolved from the production and analysis of genetically engineered mouse strains.

Dr. Mak has received several awards and honors for his work. He is a member of the Order of Ontario and was elected as a foreign associate to the National Academy of Sciences in the discipline of immunology in 2002. Dr. Mak has received the King Faisal Prize for Medicine, the Gairdner Foundation International Award, the Paul Ehrlich Prize, the Novartis Prize in Immunology, the Killam Prize by the Canada Council for the Arts, and the Sloan Prize of the General Motors Cancer Foundation, and the Robert L. Noble Prize by the National Cancer Institute of Canada.

Thursday, May 24

SESSION 3A:

Immuno-Oncology

SPONSORED BY: AstraZeneca, CDRD, Merck, Roche

Chair: Pamela Ohashi, Princess Margaret Cancer Centre

CAR Therapy: The CD19 Paradigm and Beyond

Michel Sadelain, MD, PhD, Center for Cell Engineering, Memorial Sloan Kettering Cancer Center, New York, NY, USA

Chimeric antigen receptors (CARs) are synthetic receptors that redirect and reprogram T cells to mediate tumor rejection. The most successful CARs used to date are those targeting CD19, which offer the prospect of complete remissions in patients with chemorefractory/relapsed B cell malignancies, especially acute lymphoblastic leukemia (ALL). We have treated 53 adult patients with refractory and relapsed ALL with autologous peripheral blood T cells manufactured to express the 19-28z CAR. Despite a high complete remission rate (83%), a number of patients will eventually relapse, pointing to the need to further improve CAR design and T cell engineering. To enhance the intrinsic (function, persistence) and extrinsic (action on the tumor microenvironment) potency of adoptively transferred T cells, we have designed novel CARs to delay the onset of T cell exhaustion and recruit tumor-infiltrating T cells via *trans*-costimulation. Using CRISPR/Cas9, we found that directing a CAR to the T cell receptor alpha chain (*TRAC*) locus not only results in uniform CAR expression in human peripheral blood T cells, but enhances T cell potency by attenuating CAR tonic signaling and further postponing T cell exhaustion, enabling *TRAC*-CAR T cells to vastly outperform conventionally engineered CAR T cells. We also recently succeeded in modeling cytokine release syndrome (CRS), one of the major complications of CD19 CAR therapy, pinpointing macrophages as the major source of pathogenic cytokines such as interleukin-6. In aggregate, these findings hold the promise for further improving CD19 CAR therapy and the development of CAR T cells for other cancers.

Michel Sadelain
Michel Sadelain, MD, PhD, is the Director of the Center for Cell Engineering and the incumbent of the Stephen and Barbara Friedman Chair at Memorial Sloan-Kettering Cancer Center. He is a Member of the Immunology Program and the Departments of Medicine and Pediatrics.

Dr. Sadelain's research focuses on human cell engineering and cell therapy to treat cancer and hereditary blood disorders. His laboratory has made several seminal contributions to the field of chimeric antigen receptors (CARs), from their conceptualization and optimization to their clinical translation for cancer immunotherapy. His group was the first to publish dramatic molecular remissions in patients with chemorefractory acute lymphoblastic leukemia following treatment with autologous CD19-targeted T cells.

Dr. Sadelain is the recipient of the Cancer Research Institute's Coley Award for Distinguished Research in Tumor Immunology, the Sultan Bin Khalifa International Award for Innovative Medical Research on Thalassemia and NYPLA Inventor of the Year award. He previously served on the NIH Recombinant DNA Advisory Committee and as President of the American Society for Gene and Cell Therapy.

A Trans-Canada Highway for CAR-T Cells

Brad Nelson, Ph.D., Distinguished Scientist and Director, Deeley Research Centre, Co-Director, Immunotherapy Program, BC Cancer, Victoria BC, Canada

The striking clinical successes of cancer immunotherapy are transforming oncology, yet they

also bring significant clinical and fiscal challenges for publicly funded healthcare systems in Canada and beyond. In particular, a new cell-based therapy involving Chimeric Antigen Receptor (CAR) T cells is yielding up to 90% complete response rates against B cell leukemias yet comes at a commercial cost exceeding $500,000 per patient. Fortunately, the Canadian immunotherapy research community has a strong history of innovation and collaboration, which positions the country to excel in this new era. I will discuss how CAR-T cells work, why they are a game-changer for oncology, and the opportunities and challenges we face in applying this approach to other cancers. I will describe an exciting new initiative to create a national, public sector CAR-T cell program, which will leverage Canadian talent and innovation while enabling greater cost control for our healthcare systems.

Brad Nelson
Dr. Nelson is a native of Vancouver BC. He received his B.Sc. from the University of British Columbia in 1987 and Ph.D. from the University of California at Berkeley in 1991. He completed postdoctoral training with Dr. Phil Greenberg and held faculty positions at the Fred Hutchinson Cancer Research Center and University of Washington in Seattle. In 2003, he became the founding Director of BC Cancer's Deeley Research Centre in Victoria BC. He is a Professor of Medical Genetics at the University of British Columbia and a Professor of Biochemistry/Microbiology at the University of Victoria. Dr. Nelson's lab uses genomic and molecular approaches to study the immune response to cancer, with an emphasis on ovarian cancer. As Co-Director of BC Cancer's Immunotherapy Program, he is leading a phase I clinical trials program focused on adoptive T cell therapy for gynecological cancers, leukemia, lymphoma, and other malignancies.

A New Generation CAR Containing a JAK–STAT Signaling Domain Mediates Superior Antitumor Effects

Naoto Hirano, Princess Margaret Cancer Centre, University Health Network, Toronto, ON

The adoptive transfer of T cells engineered to express a chimeric antigen receptor (CAR) specific for the B lymphocyte antigen CD19 has shown remarkable clinical responses in patients with refractory B cell malignancies. Late 2017, FDA approved tisagenlecleucel-T (Kymriah™, Novartis) and axicabtagene ciloleucel (Yescarta™, Kite Pharma) for the treatment of refractory and relapsed pediatric acute lymphoblastic leukemia and advanced non-Hodgkin lymphoma, respectively. However, the therapeutic effects of CAR-T cells that target other malignancies have not yet resulted in significant clinical benefit.

Although suboptimal tumor trafficking and a variety of immunosuppressive mechanisms can thwart CAR-T cell effector responses, the signals delivered by the current CAR constructs may still be insufficient to optimally activate antitumor T cell functions. Full T cell activation and proliferation requires multiple signals, including T cell receptor (TCR) engagement (signal 1), co-stimulation (signal 2) and cytokine engagement (signal 3). However, CAR constructs currently being tested in the clinic contain a CD3ζ (TCR signaling) domain and co-stimulatory domain(s) but not a domain that transmits signal 3.

We have developed a novel CAR construct capable of delivering cytokine signaling in an antigen-specific manner[3]. Our new-generation CD19 CAR encodes a truncated intracellular domain from the interleukin (IL)-2 receptor β-chain (IL-2Rβ) and a STAT3-binding tyrosine-X-X-glutamine (YXXQ) motif, along with the TCR signaling (CD3ζ) and co-stimulatory (CD28) domains (28-ΔIL2RB-z(YXXQ)). The 28-ΔIL2RB-z(YXXQ) CAR-T cells showed antigen-dependent activation of the JAK kinase and of the STAT3 and STAT5 transcription factors signaling pathways, which enhanced their proliferation and prevented terminal differentiation *in vitro*. The 28-ΔIL2RB-z(YXXQ) CAR-T cells demonstrated better *in vivo* persistence and antitumor effects in various tumor models as compared with CAR-T cells expressing a CD28 or 4-1BB co-stimulatory domain alone. These results suggest that our new-generation CAR has the potential to demonstrate superior antitumor effects with minimal toxicity in the clinic and that clinical translation of this novel CAR is warranted.

1. Park JH et al. N Engl J Med. 2018;378(5):449-459
2. Maude SL et al. N Engl J Med. 2018;378(5):439-448
3. Kagoya Y et al. Nat Med. 2018;24(3):352-359

Naoto Hirano
Dr. Hirano received his MD and PhD from the University of Tokyo and did his post-doctoral training at the Dana-Farber Cancer Institute, Harvard Medical School with Dr. Lee M. Nadler. Before

moving to Toronto in 2011, Dr. Hirano was Assistant Professor of Medicine at the Harvard Medical School. He is currently Senior Scientist at the Princess Margaret Cancer Centre, and Associate Professor of Medicine in the Department of Immunology at the University of Toronto. He is also Associate Director for Research of the Tumor Immunotherapy Program at the Princess Margaret Cancer Centre.

The overarching goal of Dr. Hirano's research is to devise novel anti-tumor immunotherapeutic modalities that can cure cancer. His laboratory is particularly interested in understanding how the interactions between T cells and antigen-presenting cells affect priming, expansion, persistence and differentiation of T cells. He also seeks to clarify how this leads to the subsequent generation and maintenance of T cell memory.

Dr. Hirano has received prestigious awards and honors including the American Society of Hematology Scholar Award and Ontario Institute for Cancer Research (OICR) Investigator Award (renewed). His research has been supported by multiple funding mechanisms including NIH, CIHR, OICR, Networks of Centres of Excellence (BioCanRX), Terry Fox Research Institute, Canada First Research Excellence Fund (Medicine by Design), and Princess Margaret Cancer Foundation. Dr. Hirano has been Editorial Board Member of the Cancer Immunology Research journal.

Immuno-Oncology Combinations in Clinical Development

Lillian L. Siu, MD, BMO Chair in Precision Genomics, Professor of Medicine, Princess Margaret Cancer Centre, Toronto, Canada

An emerging pipeline of immuno-oncology (IO) therapeutics has entered clinical testing, such as immune checkpoint inhibitors beyond anti-CTLA4 and anti-PD-1/L1 antibodies, costimulatory molecules, inhibitors of regulatory T cells, cancer vaccines using individual neoantigens, functional modifiers of immunosuppressive enzymes, myeloid cell modulators, adoptive cell therapy, as well as conventional therapies inducing antigen release and immunogenic cell death, among others. The potential number of combinations using these various IO therapeutics is considerable, such that the selection of the most scientifically rational combinations to proceed to clinical development is critical to ensure appropriate use of patients, resources and infrastructure. The dearth of nonclinical models that can reliably reflect the human immune system and microenvironment further complicates this selection, resulting in clinical combinations that lack scientific hypothesis or are based largely on empiricism. The go-no-go decisions at the end of early evaluations of IO combinations represent another challenge as patient populations enrolled are typically heterogeneous and no validated predictive biomarkers of sensitivity or resistance currently exist with IO therapeutics. Using examples of IO combinations tested to date, this presentation will focus on present trends and future predictions, providing some key points on how the clinical development of these compounds can be modernized and streamlined. For instance, adaptive design elements to allow enrichment of sensitive disease subtypes, and adaptive randomization strategies, can be applied to combinatorial studies of these compounds to accelerate their development.

Lillian L. Siu

Dr. Siu is a senior medical oncologist at Princess Margaret Cancer Centre since 1998, and has been a Professor of Medicine at the University of Toronto since 2009. She is the Director of the Phase I Program and Co-Director of the Bras and Family Drug Development Program at Princess Margaret Cancer Centre, and holds the BMO Chair in Precision Genomics (2016-2026). She is also the Clinical Lead for the Tumor Immunotherapy Program at Princess Margaret Cancer Centre. Dr. Siu served on the Board of Directors for the American Society of Clinical Oncology (ASCO) for a four-year term (2012-2016). She also served as a member of the Nomination Committee for the American Association for Cancer Research (AACR) (2014-2016). She currently serves on the AACR Board of Directors for a three-year term (2017-2020).

Dr. Siu’s major research focus is in the area of new anticancer drug development, particularly with respect to phase I trials and head and neck malignancies. She is the Principal Investigator of a phase I cooperative agreement UM1 award (2014-2019) sponsored by the United States National Cancer Institute. IIn addition to her active research in early phase clinical trials, she has been leading genomics initiatives and immuno-oncology trials at the Princess Margaret Cancer Centre. Together, the three programs of drug development, cancer genomics and tumor immunotherapy form a triad of

synergy that supports the institution's core vision to deliver precision cancer medicine.

Internationally, Dr. Siu was the recipient of the US NCI Michaele C. Christian Award in Oncology Drug Development in 2010. Locally, she was awarded the University of Toronto Department of Medicine Eaton Scholar Researcher in 2016. She was the ASCO Conquer Cancer Foundation Grants Selection Committee Chair in 2009-10. She was Chairperson of the AACR Education Committee, Co-Chairperson of the Scientific Committee for the 2012 Annual Meeting and Co-Chairperson for the Clinical Trials Committee 2015-2017. Dr. Siu has published over 270 peer-reviewed manuscripts, and she is currently a scientific editor for *Cancer Discovery* and is on the editorial board for *JAMA Oncology*.

PANEL MEMBERS

Jian Wang, MD, PhD, Biologics and Genetic Therapies Directorate, Health Canada

Dr. Jian Wang has been the Chief of Clinical Evaluation Division for the past 13 years and manages a team of clinical and medical evaluators. His division has regulatory responsibility for assessing non-clinical, PK/PD and clinical data for biological drugs for the treatment of haematological, oncological, and infectious diseases. Radiopharmaceuticals, gene therapies and biosimilars are also regulated by his division. He actively participates in various Health Canada, ICH, WHO, APEC and DIA working groups and expert committees.

Dr. Wang received his MD from Harbin Medical University, China and was awarded PhD in Physiology from the University of British Columbia, Canada. He joined Health Canada in 1996 with many years of scientific and clinical research experience in both academic and clinical settings.

Ismael Samudio, CDRD

Ismael Samudio obtained his Ph.D. in genetics from Texas A&M University (2002), where he investigated the mechanisms of non-canonical estrogen receptor signaling in breast cancer cells, with particular interest in chromatin remodeling and estrogen receptor/Sp1 interactions. After postdoctoral training at the Institute of Biotechnology in Houston, Ismael joined the Section of Molecular Hematology at MD Anderson Cancer Center in 2004 as a Research Scientist where he led investigations on the antileukemic and antitumor effects of synthetic triterpenoids, guggulipids, bcl-2 inhibitors, targeted peptides, p53 activators and kinase inhibitors. In 2007 he was promoted to Research Instructor in the Department of Stem Cell Transplantation and Cellular Therapy at MD Anderson Cancer Center, where he made the seminal discoveries that mitochondrial uncoupling was the basis for the observed Warburg effect in leukemia cells, and that pharmacological inhibition of fatty acid oxidation was an effective therapeutic strategy to sensitize leukemia stem cells to chemotherapy induced cell death. In addition, in collaboration with Dr. Michael Andreeff and Dr. Frank Marini, he demonstrated the therapeutic efficacy of gene-modified mesenchymal stromal cells in animal models of pancreatic and ovarian cancer.

In 2009 Ismael joined Pontifical Javeriana University in his home country of Colombia as an Associate Professor where he continued to pursue metabolic strategies for the treatment of human cancer, including a compassionate use study of the antidiabetic agent metformin in combination with metronomic chemotherapy that revealed a potential immunomodulatory effect of metformin in advanced cancer patients. In 2013 Ismael joined the laboratory of Gerry Krystal at the BC Cancer Agency to receive additional postdoctoral training in immunotherapy, where he discovered that Herpes virus Simplex-1 is a potent activator of NK function and can be an adjuvant in the setting of bone marrow transplantation for the treatment of leukemia.

In 2015 Ismael joined CDRD as an Immunotherapy Scientist where he participated in the development of various immunotherapy platforms, including a novel targeting arm for CAR-T cells that can potentially enable therapeutic efficacy against various solid tumors, and in 2016 assumed the leadership of the Biologics Division. Ismael has published over 70 peer reviewed articles and various book chapters on the use of small molecules, cellular therapeutics, and immunotherapy strategies for the treatment of cancer, and is a leading expert on tumor metabolism.

Thursday, May 24

SESSION 3B:

The Gut Microbiome as a Novel Therapeutic Target

Chair: Brad Urquhart, Western University

Overview of the Microbiome and its Potential Role in Therapeutics

Michael G Surette, Professor, Canada Research Chair in Interdisciplinary Microbiome Research, Farncombe Family Digestive Health Research Institute, Michael G. DeGroote Institute for Infectious Disease Research, McMaster University, Hamilton ON Canada

The human body is host to numerous complex microbial communities at different body sites that comprise the human microbiome. These microbes and their dynamic interactions with each other and with the host play critical roles in human development and health. The microbiome plays critical roles in normal development, digestion/nutrition and maintenance of immune homeostasis. However, bacteria within the microbiome also contribute to disease: as pathogens, as reservoirs of antibiotic resistance and virulent genes and, when these microbial communities become out of sync with their host, as drivers of chronic inflammatory diseases. The study of the microbiome has mostly been driven by culture-independent DNA sequencing approaches. There is a prevailing view that much of the human microbiome (and microbial diversity in general) is not readily accessible to cultivation in the laboratory. Many studies are challenging this dogma and we have established culture strategies that capture the diversity of the microbiota of the gastrointestinal and respiratory tracts. Importantly, we demonstrated that a greater diversity of microbiota is revealed by combining culture with molecular methods than by culture-independent methods alone. Moreover, our data has allowed us to define simple conditions for targeted enrichment of specific taxa of interest. We are combining these approaches with genomics and culture-enriched metagenomics to explore the diversity and functionality of the human microbiome. Culturing provides access to the rich diversity of the microbiome and facilitates bioprospecting the microbiome for novel therapeutic potential.

Michael G Surette
Michael G. Surette is Professor of Medicine and Biochemistry, and Canada Research Chair in Interdisciplinary Microbiome Research in the Farncombe Family Digestive Health Research Institute and Michael G. DeGroote Institute for Infectious Disease Research at McMaster University. His group researches the human microbiome of the airways and gut in health and disease. The lab is focused on high throughput culturing and phenotyping methods combined with next-generation sequencing approaches to investigate infectious disease and the microbiome, and changes in the microbiome across the life span. Specific diseases researched include cystic fibrosis, asthma, pneumonia, ulcerative colitis, and irritable bowel syndrome.

Microbial Effects on Innate and Adaptive Immunity

Kathy D. McCoy, University of Calgary

The intestinal microbiome plays a critical role in shaping the development and function of innate immune cells at both mucosal and systemic sites. Although host-microbial interactions throughout life are critical for maintaining homeostasis and regulating the immune system, these interactions are likely to be especially important in early life. The dynamics of early life microbial colonization plays an important role in development of the immune system and can critically influence susceptibility to a variety of immune-mediated diseases later in life. Changes in microbial composition during early life when the immune system is still developing have

been demonstrated to be particularly important, suggesting a critical window of opportunity for proper conditioning of the immune system. While live microbes are very efficiently contained to mucosal sites, systemic exposure to microbial products or metabolites is ubiquitous and exposure to maternal microbiota-derived metabolites can even occur *in utero*. We utilize gnotobiotic mouse models in an effort to gain greater insight into the multiple mechanisms by which the intestinal microbiota determines the function of innate and adaptive immune cells and promotes homeostasis. A deeper understanding of the underlying molecular and cellular pathways involved is required in order to harness the power of the microbiome to treat or prevent disease.

Kathy McCoy

Dr. Kathy McCoy, PhD, is a Professor in the Dept. of Physiology & Pharmacology, Cumming School of Medicine, member of the Snyder Institute for Chronic Disease, and scientific director of the International Microbiome Centre at the University of Calgary. Her lab is interested in the dynamic interplay between the gut microbiota and the innate and adaptive immune systems. Using germ-free and gnotobiotic mouse models her research group aims to understand how exposure to intestinal microbes early in life educates and regulates the developing immune system and how this impacts on susceptibility to immune-mediated diseases such as allergy and autoimmunity. Her lab studies microbiome-immune interactions in health and diseases and aims to elucidate the molecular mechanisms by which the commensal microbiota influences host immunity.

Fecal Microbial Transplants: Treatment of C. Difficile and Beyond

Michael Silverman, Western University

Historically the organisms within the gut were not considered important physiologically. Awareness of the importance of the gut "microbiome" was first raised by the potentially life threatening problem of *Clostridium difficile* infection which could be triggered by antibiotics which damage the normal microbiome and allow this pathogen to overgrow. Recently the impact of the gut microbiome on many other common medical problems has been highlighted; including not just in gastroenterology but even including endocrinology, cardiology, neurology, rheumatology and psychiatry. Fecal Transplants are both a high tech and extremely low tech solution to the problem of an altered microbiome. We will outline the basic mechanisms by which something previously thought of as "just crap" can impact diverse physiological processes, and the potential for therapeutic alteration of the gut microbiome in the treatment and prevention of human disease.

Michael Silverman

Training:

- Medical School and Internal Medicine Residency: University of Toronto.
- Infectious Diseases Fellowship: University of Manitoba
- HIV Postdoctoral Research Fellowship: University of California, San Francisco.
- Board Certified: Internal Medicine and Infectious Diseases

Clinical and Academic Activities:

- Chair/Chief of Infectious Diseases, Western University
- Medical Director of the HIV Clinic, St Joseph's Hospital
- Co-Director of Infection Control, London Health Sciences and St Joseph's Hospital
- POEM (Program of Experimental Medicine) Scientist
- Assistant Professor of Global Health, Dalla Lana School of Public Health, University of Toronto

Major Research Interests:

- Gut Microbiome and Fecal Microbial Transplantation
- Prevention of Mother to Child Transmission of HIV
- Factors Driving Inappropriate Antibiotic Prescribing in Community Practice
- Infections in Marginalized Populations

Unexplained Atherosclerosis and Metabolic Products of the Intestinal Microbiome

J. David Spence M.D., Professor of Neurology and Clinical Pharmacology; Stroke Prevention & Atherosclerosis Research Centre, Robarts Research Institute; Western University, London, Ontario

Background and Aims: There is increasing awareness that the intestinal microbiome plays an important role in human health. We investigated its

role in the burden of carotid atherosclerosis, measured by ultrasound as total plaque area.

Methods: Multiple regression with traditional risk factors was used to identify three phenotypes among 316/3,056 patients attending vascular prevention clinics. Residual score (RES; i.e. the distance off the regression line, similar to standard deviation) was used to identify the 5% of patients with much less plaque than predicted by their risk factors (Protected, RES <-2), the 90% with about as much plaque as predicted (Explained, RES -2 to 2) and the 5% with much more plaque than predicted (Unexplained RES >2). Metabolic products of the intestinal microbiome that accumulate in renal failure – gut-derived uremic toxins (GDUT) – were assayed in plasma by ultra-performance liquid chromatography coupled to quadrupole time-of-flight mass spectrometry.

Results: Plasma levels of trimethylamine n-oxide (TMAO, derived largely from egg yolk and red meat), and p-cresyl sulfate, p-cresyl glucuronide, and phenylacetylglutamine (derived from amino acids) were significantly lower among patients with the Protected phenotype, and higher in those with the Unexplained phenotype, despite no significant differences in renal function or in dietary intake of nutrient precursors of GDUT. In linear regression with a broad panel of risk factors, TMAO ($p = 0.015$) and p-cresyl sulfate ($p = 0.016$) were significant independent predictors of carotid plaque burden. Plasma levels of GDUT were significantly higher with even modest renal impairment, were associated with higher carotid plaque burden, and were not related to Mediterranean diet scores.

Conclusions: The intestinal microbiome appears to play an important role in atherosclerosis. These findings raise the possibility of novel approaches to treatment of atherosclerosis such as fecal transplantation and probiotics. Patients with renal impairment, including the elderly, should avoid egg yolk and limit intake of animal flesh, particularly red meat.

*Co-authors: Chrysi Bogiatzi M.D., Gregory Gloor Ph.D., Emma Allen-Vercoe Ph.D., Gregor Reid Ph.D., Ruth G. Wong M.Sc., Bradley L. Urquhart Ph.D., Vincent Dinculescu M.D., Kelsey N. Ruetz BMSc., Thomas J. Velenosi PhD, Michael Pignanelli BMSc., Caroline Just M.D.

J. David Spence

Professor Spence has focused on stroke prevention since his second year of Neurology residency with Dr. Henry Barnett. He realized then that half of the ~ 1000 strokes he had seen were due to hypertension, and therefore entirely preventable. He studied Zoology and then Medicine at Western University, obtained Royal College Fellowships in both Neurology and Internal Medicine at Western, and completed a fellowship in Clinical Pharmacology at the Cardiovascular Research Institute, University of California at San Francisco. He then returned to Western in 1976, opening the third hypertension Clinic in Canada in 1977. By 1983, due to efforts by the Department of Family Medicine in cooperation with his clinic, strokes in the London area were down by half.

He pioneered the measurement of 2-dimensional carotid total plaque area beginning in 1990, and since 1994 has collaborated with Prof. Aaron Fenster and Dr. Grace Parraga at the Robarts Research Institute in measurement of 3D plaque volume, plaque ulceration and assessment of vulnerable plaque. He also pioneered a new approach to vascular prevention – "treating arteries instead of treating risk factors", that has markedly reduced risk among high-risk patients with carotid stenosis. His research program focuses on measurement of atherosclerosis by ultrasound, for patient management, genetic research and for assessing effects of new therapies. Other areas of expertise include vitamin therapy for homocysteine, the clinical pharmacology of stroke prevention, physiologically individualized therapy for resistant hypertension, nutrition in stroke prevention and identification of high-risk asymptomatic carotid stenosis. He has seen over 40,000 patients at high risk of stroke, preventing ~ 10,000 strokes personally, but by his research, publications and over 600 lectures on stroke prevention to thousands of physicians in 39 countries has been able to accomplish much more. Despite a busy clinical practice, his publications include 4 books and over 450 peer-reviewed publications, with with an H-index of 78 on Google Scholar, i-10 index 263.

Thursday, May 24

SESSION 3C:

Practical Pharmacology: Case Studies from Across the Country

Chair: George Dresser, Western University

Clearing Up Controversies around Carfentanil

Jessica L.S. Leen, MD, FRCPC, University of Toronto

This talk will provide an overview of our current understanding of carfentanil, a specific fentanyl analogue, centred around a case. Topics include the history of the drug as an animal tranquilizer to its current role as a potent adulterant of illicit drugs. Attendees will develop a working knowledge of carfentanil's pharmacology based on animal studies and case reports. Controversies to be clarified include detection challenges and appropriate first responder safety precautions.

Jessica L.S. Leen
Jessica L S Leen is a Royal College of Physicians and Surgeons of Canada certified general internist who completed her core training and medical school at the University of Toronto. She is currently completing her final year of her internal medicine subspecialty fellowship in Clinical Pharmacology and Toxicology. Her areas of focused interest include addiction medicine, specifically opioid substitution therapies, therapeutic use of cannabinoids as opioid-sparing agents, and adverse drug reactions. Her career goals include improving the care of the patient with addictions and promoting the value of clinical pharmacology in the community. In her off time, she enjoys painting, yoga and cooking.

A Case of Unilateral Adrenal Adenoma with Resistant Hypertension

Marc L Chretien, George K Dresser
Division of Clinical Pharmacology and Toxicology, Department of Medicine, Western University

We discuss a case of a 60-year-old gentleman with history of resistant hypertension and hypokalemia who was referred to outpatient clinic for workup and management of suspected secondary hypertension. Initial interview revealed ~20-year history of worsening hypertension, with associated hypertensive nephropathy, and obesity, without history of diabetes mellitus, no angina-like symptoms or history of acute coronary syndromes, no cerebrovascular accidents, no obstructive sleep apnea, no smoking and no alcohol use/abuse. At initial assessment, the patient's antihypertensive medications included - chlorthalidone 25 mg daily, amlodipine 10 mg daily, coversyl 8 mg daily, metoprolol 75 mg bid, spironolactone 25 mg daily. Physical examination showed supine blood pressure 178/84, pulse 68, weight 104.9 kg, with normal heart sounds, no enlarged or displaced apex, no abdominal bruits, and unremarkable fundoscopy. Initial bloodwork showed serum potassium 3.6, serum creatinine 146, serum renin 5.2, serum aldosterone 973, serum cortisol 438. CT adrenals showed 1.2 cm left adrenal nodule. Follow-up venous sampling showed serum aldosterone distal IVC 1,270 (pmol/L), proximal IVC 5,820, left renal vein 5,760, left adrenal vein >27,000, right renal vein 974. Sampling from right hepatic vein, near location of right adrenal vein drainage, showed serum aldosterone 682. Serum cortisol sampled at all sites was within normal limits. The patient completed laparascopic left adrenalectomy for left adrenal Conn's tumor. A review of current literature and treatment guidelines provides a framework for clinical decision making in this scenario.

Improving Outcomes for Childhood Cancer Patients Using Genomics-Guided Treatment Optimization

Catrina M Loucks, Division of Translational Therapeutics, Department of Pediatrics, Faculty of Medicine, University of British Columbia, Vancouver, BC, Canada

While the 5-year survival rates for children with cancer continue to improve, the major problem of drug-related toxicities remains. Drug-related toxicities resulting from cancer treatment have long been regarded as necessary risks, balanced by the hope of curing a potentially fatal disease. Importantly, pharmacogenomics, the study of how genetic variability contributes to individual drug responses, works to identify individual genetic differences that can help predict a patient's risk of developing serious drug-related toxicities before a drug is administered. The Canadian Pharmacogenomics Network for Drug Safety (CPNDS) was established in 2004 with a mission to improve drug safety, and through a personalized medicine project, the CPNDS has successfully implemented genomic testing across British Columbia to predict the risk of three drug-related toxicities in childhood cancer. The introduction of genomic testing into clinical practice provides clinicians with an additional tool to select the safest and most effective treatment strategy for patients. Knowing who is at higher risk prior to cancer treatment means that alternative treatment strategies can be considered, dosing can be adjusted in some cases, and monitoring for the development of drug-related toxicities can be enhanced. Furthermore, knowing who is at lower risk prior to cancer treatment can provide reassurance for both clinicians and families when considering aggressive therapy. For example, for a 12-year-old boy treated at BC Children's Hospital who relapsed one year post-treatment, the treatment that promised the greatest chance of survival included anthracyclines that are often accompanied by the severe drug-related toxicity of cardiac dysfunction (cardiotoxicity). Upon genomic testing, this boy was found to be at low risk for developing cardiotoxicity based on his individual genetics, providing reassurance to initiate anthracycline-based therapy, while balancing hope for survival with risk of toxicities. Importantly, through this work the CPNDS hopes to further genomics-based interventions that reduce the burden of drug-related toxicities in the treatment of childhood cancer.

Catrina M Loucks
Catrina is a postdoctoral fellow working with Dr. Bruce Carleton and the Canadian Pharmacogenomics Network for Drug Safety (CPNDS) to understand how genetic variation contributes to the likelihood of developing drug-related toxicities, especially in childhood cancer treatment. Catrina has experience uncovering genetic causes for rare disorders from her Bachelor of Health Sciences (BHSc) and subsequent MSc work at the University of Calgary, under the supervision of both Dr. Micheil Innes and Dr. Jillian Parboosingh. She then sought to explore functional impacts of uncovered genetic mutations by pursuing a PhD under the supervision of Dr. Michel Leroux at Simon Fraser University, using the simple roundworm, *C. elegans*, as a model. To understand how genetic information can be used to improve the clinical care of patients, Catrina will incorporate genetic predictors of drug-related toxicities associated with childhood cancer treatment into predictive genetic tests that can be used by clinicians and families to assess the risks and benefits associated with specific drug treatments.

Choosing the Right Antihypertensives for your Pregnant Patient

Albayada Medhar, Western University

Objectives: Classification and diagnosis of hypertension disorders in pregnancy, and management of hypertension in pregnancy and postpartum.

Hypertension is a highly prevalent condition in pregnancy, yet we have a limited data giving the challenges of conducting studies on this unique population.

I will be presenting the new Hypertension Canada's 2018 Guidelines for the Management of Hypertension in Pregnancy.

Albayda Mehdar
Albayda Mehdar is a current fellow in clinical pharmacology and toxicology program at University of Western. She finished her internal medicine training at the University of Toronto with plans to pursue further training in obstetric medicine.

CSPT Clinical Fellowship Award Lecture

Genetic Screening and Cannabis Induced-Psychosis: Who, What and When?

Gavin Sun, Division of Clinical Pharmacology and Toxicology, Western University, London, ON

There is a high likelihood of cannabis being legalized in Canada. With such a change in policy, it is expected that there will a subsequent increase in consumption of the substance. In other jurisdictions where legalization permitted a subsequent increase in usage, an increased incidence of cannabis-related morbidity has been reported.

Genomic profiling has identified individuals with higher risks of development of cannabis induced psychosis. While barriers currently exist in the availability of such testing, with cannabis induced psychosis one of the major worrisome sequelae from cannabis use and given the anticipated increase in consumption, it may be of value to implement genetic screening for certain cohorts of potential cannabis consumers.

Objectives of presentation

1. Review the pathophysiology of cannabis induced psychosis
2. Discuss the clinical presentation of cannabis induced psychosis
3. Review genetic screening targets to identify those at risk for the subsequent development of cannabis induced psychosis

Gavin Sun

Dr Sun is currently in his final year of fellowship in Clinical Pharmacology and Toxicology at Western University in London, Ontario. He was born and raised in Johannesburg, South Africa and graduated with an MD from the University of the Witwatersrand in 2006. He subsequently completed my 2 years of internship and 1 year of community service in South Africa in 2009. He emigrated to Canada in 2010 and practised in rural Alberta for 3-and-a-half years. A long-term goal was to pursue specialist medicine and he was accepted into a medicine residency at the University of Calgary in July 2013. He completed his core Internal Medicine training in Calgary and subsequently started a Clinical Pharmacology fellowship in London in 2016. His practice interests include vascular health, acute toxicology, factors driving prescribing behavior and clinical implementation of pharmacogenomics.

CSPT Post-Doctoral Award Lecture

Pharmacogenomics for Neurological Conditions and Related Phenotypes

Galen Wright, Canadian Pharmacogenomics Network for Drug Safety (CPNDS), University of British Columbia, Vancouver, BC

Neurological disorders present a high health care burden on society and are becoming of increasing concern with an aging global population. Adding to this burden, numerous medications are associated with adverse drug reactions that influence the nervous system, causing debilitating drug-induced neurotoxicities. With ready access to genomic technologies, pharmacogenomics is beginning to make important advances in identifying genetic variants that contribute towards inter-individual risk to adverse drug reactions. For example, it has recently been shown that a high proportion (i.e. 97%) of individuals carry clinically-meaningful pharmacogenomic variants, indicating the important role that genetic variation plays in drug response. For over a decade, the Canadian Pharmacogenomics Network for Drug Safety has been involved in various neurological pharmacogenomic studies, including research into analgesic-related toxicities, severe cutaneous reactions from antiepileptics, immunomodulatory agents in multiple sclerosis and neurotoxicities from cancer medications. This presentation will discuss how pharmacogenomics can aid in the treatment of neurological conditions and related phenotypes by identifying biomarkers of

clinical relevance, in addition to increasing our understanding of the biological mechanisms underlying these reactions. Additionally, the overlap existing between the genes influencing drug-induced neuropathies and those that heritable neuropathy conditions will be discussed. Ultimately, such research will contribute towards moving pharmacogenomic tests into clinical care to provide safer and more effective treatment solutions.

Galen Wright

Galen Wright is a researcher at the Canadian Pharmacogenomics Network for Drug Safety (CPNDS), University of British Columbia. His research interests lie in the fields of pharmacogenomics, clinical pharmacology and bioinformatics. Dr. Wright completed his PhD in Genetics at Stellenbosch University, where his research involved characterizing genes that are involved in antipsychotic response in African populations. His current research projects include investigating serious adverse drug reactions from chemotherapeutic agents as well as those caused by medications used to treat neurologic conditions. This work has led to the identification of predictive biomarkers for drug-induced neurotoxicities, liver injury and severe cutaneous reactions. Dr. Wright has been supported by various funding organizations, including the Canadian Institutes of Health Research and the Drug Safety and Effectiveness Cross-Disciplinary Training Program. To date, he has published 28 peer-reviewed manuscripts and was recently awarded the 2016 Canadian Society of Pharmacology and Therapeutics Publication Award.

Thursday, May 24

SESSION 4A:

Translational Medicine

SPONSORED BY: AstraZeneca, Merck, Roche

Co-Chairs:Ming Tsao, Ontario Cancer Institute, and Janet Dancey, Canadian Cancer Trials Group, and Queen's University

Opening Pandora's Genome: Rethinking Molecular Diagnostics

Aly Karsan, MD, FRCPC, Medical Director, Centre for Clinical Genomics, Genome Sciences Centre, British Columbia Cancer Agency, and Professor, Pathology & Laboratory Medicine, University of British Columbia, Vancouver, BC

Tumors are currently classified based on tissue or organ of origin and then further subclassified by morphology and immunohistochemistry. Increasingly, specific genetic changes are being associated with tumor subtypes and by extension with therapeutic subclasses. As more genetic events are being associated with different tumor types, it is becoming critical to evaluate different genetic events in order to reveal potential treatments for individual cancers. In some cases identification of specific genetic events define a contraindication to a particular class of targeted therapy. The ability to select the right patient for the right treatment at the right time forms the basis of precision medicine. Genetic testing refers to testing a single gene or part of gene, while genomic testing refers to testing the entirety of the genome. Use of the term genomic testing is sometimes coopted to refer to the testing of large numbers of genes simultaneously (not necessarily whole genome), and this is also referred to as gene panel testing. Mutation frequencies vary more than 1000-fold across different cancers. Because genomic testing can identify many different variants, not all of which have a clinical impact, proper interpretation of variants is important. The ability to test many genes for variants has become clinically tractable through the use of next-generation sequencing. In this presentation I will focus on the use of next-generation sequencing in diagnosis and prediction of treatment response, and discuss some of the issues surrounding implementation of genomic testing.

Aly Karsan

Aly Karsan is Professor of Pathology and Laboratory Medicine, University of British Columbia, the Medical Director of the Cancer Genetics & Genomics Laboratory, and the Medical Director for the Centre for Clinical Genomics at the Genome Sciences Centre, at the British Columbia Cancer Agency. The Centre for Clinical Genomics, which is embedded within the Genome Sciences Centre comprises pathologists, clinical and basic scientists with genetics and genomics expertise, and bioinformaticians, as well as a social scientist and health economist. He received his MD from Queen's University at Kingston, completed his residency in Hematological Pathology at the University of British Columbia, which was followed by a research fellowship at the University of Washington in Seattle. He has a major interest in developing next-generation sequencing approaches for application in the clinic. This work led to the clinical implementation of the first CAP-compliant next-generation sequencing test in Canada.

As a Clinician-Scientist of the Canadian Institutes of Health Research, and a Senior Scholar of the Michael Smith Foundation for Health Research, his research interests focus on functional genomics in the myeloid cancers including acute leukemia. In particular, recent research has revolved around the haploinsufficiency of microRNAs and derepression of immune signaling pathways in myeloid cancers.

His research is currently supported by grants from the Canadian Institutes of Health Research, Canadian Cancer Society Research Institute, the Heart and Stroke Foundation, Genome Canada, Genome BC, the Terry Fox Research Institute and

the BC Cancer Foundation.

Biomarker Testing in Lung Cancer

Ming S. Tsao, MD, FRCPC, Consultant Pathologist, University Health Network and Professor, Department of Laboratory Medicine and Pathobiology, Department of Medical Biophysics, University of Toronto, Toronto, Ontario, Canada.

Lung cancer accounts for approximately 30% of deaths from all cancer types in Canada, with an overall 5-year survival of 16%. Eighty percent of lung cancer belong to non-small cell lung cancer (NSCLC), with small cell lung cancer (SCLC) making up the remaining 20%. Up until 2004, chemotherapy has been the main systemic therapy available for patients with advanced stage lung cancer, which account for two-thirds of all lung cancer patients. Chemotherapy has response rates of 30-40%, yet there is no biomarker that can guide the selection of patients for this toxic therapy. The discovery of oncogenic mutations in the tyrosine kinase domain of the epidermal growth factor receptor (EGFR) gene has revolutionized the management of NSCLC patients, which now represents the poster child of personalized cancer medicine in solid tumours. Subsequent discoveries of rearrangement involving the ALK and ROS1 genes, which generated oncogenic fusion tyrosine kinases, have led to the development of additional therapies, which are highly effective for lung cancer patients whose tumours harbour these driver oncogenes. More recently, efficacious drugs with high response rates have been identified and approved for the treatment of patients with BRAF V600E mutation. With ALK, ROS1, BRAF and other upcoming novel targets being present in 1-5% of NSCLC patients, lung cancer is becoming a constellation of rare diseases, the treatment of which depends on the execution of complex biomarker testing algorithm requiring rapid turnaround time, as these patients could experience rapid clinical deterioration when treatment is delayed. New tests such as those for immune oncology therapies are rapidly being added to the testing strategy for lung cancer patients. Issues and challenges of biomarker testing in lung cancer will be discussed.

Ming Sound Tsao

Dr. Tsao is a Consultant Thoracic Pathologist, a Senior Scientist and the M. Qasim Choksi Chair in Lung Cancer Translational Research at the University Health Network, Princess Margaret Cancer Centre in Toronto. He is a Professor of Laboratory Medicine and Pathobiology, and Professor of Medical Biophysics at the University of Toronto.

Dr. Tsao is the co-chair of the Correlative Science and Tumor Biology Committee of the Canadian Cancer Clinical Trials Group (CCTG). He is a current member (and Past Chair 2011-13) of the International Association for the Study of Lung Cancer (IASLC) Pathology Committee, IASLC Staging and Prognostic Factor Committee, standing member of the Editorial Board for WHO Blue Books on Classification of Tumours 5th edition, and the Canadian Cancer Society Advisory Committee on Research. He was a past Associate Editor for the Journal of Thoracic Oncology and a member (2010-17) of the Editorial Board of Journal of Clinical Oncology. He was the lead co-editor of the IASLC Atlases of ALK and ROS1 Testing and of PD-L1 testing in Lung Cancer. He led several multi-centre studies that resulted in pan-Canadian standardization of lung predictive biomarker assays, including tests for EGFR, ALK, ROS1, PD-L1 and circulating tumor-derived EGFR T790M mutation.

Dr. Tsao received the 2011 O. Harold Warwick Award from the Canadian Cancer Society, the 2016 IASLC Mary Matthew Pathology Award, and the CCTG 2017 Dr. Joseph Pater Founder's Award for Excellence in Clinical Trials Research. He has published slightly more than 500 manuscripts and 10 book chapters. He was the Principle Investigator and Director of the CIHR/Terry Fox Foundation Specialized Training Initiative for Health Research (STIHR) Program for clinician scientists in molecular pathology of cancer, a program focused on training of next generation academic pathologists in Canada.

Tumor Mutational Burden as a Biomarker for Cancer Immunotherapy

Caitlin Connelly, Ph.D., Scientist, Foundation Medicine, Cambridge, MA

Biomarkers capable of predicting response to checkpoint inhibitor therapies represent a significant clinical need. Increased tumor neo-antigenic burden has been linked to PD1/PD-L1 therapeutic response in several conditions including metastatic melanoma, non-small cell lung carcinoma and colorectal cancer. However, the challenges and high cost associated

with neo-antigen discovery has shifted focus towards more efficient methods of response stratification. As such, tumor mutational burden (TMB) determination from whole exome sequencing and comprehensive genomic profiling has emerged as a potential solution. Specifically, clinical feasibility of TMB calculated from the FoundationOne comprehensive genomic profiling assay has been demonstrated in more than 500 patients across three disease types, including urothelial bladder carcinoma, non-small cell lung cancer, and metastatic melanoma, with case reports in glioblastoma and colorectal cancer. We detail the method utilized to establish TMB and show that targeted sequencing of 1.25 Mb provides an accurate measurement of exome-wide TMB. We describe the landscape of TMB observed from >100,000 advanced clinical cancer specimens, across > 400 cancer types and summarize the clinical performance across multiple indications. Finally, we discuss the development of an assay to measure TMB from circulating tumor DNA and retrospective analysis of clinical trial data using this bTMB assay. These data demonstrate that TMB can be accurately assessed using a clinically available CGP assay and that this biomarker can stratify patient response. Examining the landscape of TMB across a diversity of tumor types provides new data to better understand the population that can potentially benefit from immunotherapy.

Caitlin Connelly
Caitlin Connelly obtained her Ph.D. in Genome Sciences at the University of Washington (Seattle, WA). She is a Scientist in the cancer genomics group at Foundation Medicine, where she has carried out research using data from comprehensive genomic profiling of tumor specimens and cell-free DNA samples.

Molecular Diagnostic Advancement in Oncology

Alan Spatz, McGill University, McGill University Health Center & Jewish General Hospital

Effective use of targeted cancer therapies typically depends upon the identification of actionable genomics alterations, and sometimes post-translational modifications. Genomic alterations can include single-nucleotide sequence variants, insertions/deletions, chromosomal copy number variations, and somatic structural alterations. For a same molecular alteration, the testing objectives can vary and encompass the positive diagnosis of the tumor and its molecular taxonomy, its prognosis, the choice of the best therapeutic option in monotherapy, and guidance for treatment combinations. From a clinical perspective, the diversity of genomic alterations and testing objectives underlines the need to define the best molecular testing algorithm based on optimal benefit/cost ratio for a specific objective and in a specific healthcare environment. The adopted molecular testing strategy also needs to take into account the pre-analytical constraints such as tissue flows, the analytical turn-around times, and tests reimbursement. This presentation will discuss how these questions can impact the technological choice in the clinical setting. We will discuss with examples taken from solid tumors the current molecular testing options, and examine how to capitalize on the excellent collaborative network that exists in Canada to define an adaptive and sound robust molecular testing strategy. We will also discuss the importance and challenges to integrate transcriptomic and proteins assessment in cancer precision medicine.

Alan Spatz
Dr. Alan Spatz is Director of the Division of Pathology of the McGill University Health Center OptiLab that integrates academic pathology labs from the McGill University network, Professor of Pathology and Oncology at McGill University, and Director of the “X chromosome and cancer” basic research lab at the Lady Davis Institute for Medical Research. He is also the head of the Molecular Pathology research Center at the Jewish General Hospital of Montreal.

Dr. Spatz received his medical education in Lyon, France, and did his residency in Pathology in Paris at the Pierre et Marie Curie University. He worked from 1994 to 2008 at the Gustave Roussy Cancer Institute in Villejuif, France. He was strongly involved in translational and clinical research, for instance as a board member of the European Organization for Research and Treatment of Cancer (EORTC) and as the chair of the EORTC Melanoma and Pathobiology groups. He was also President of the French division of the International Academy of Pathology. He is currently co-Chair of the Melanoma committee of the Canadian Cancer Trials Group and serves as a board member of several international professional organizations, in editorial boards and strategic committees.

Dr. Spatz has created at McGill University a highly successful molecular pathology program that

integrates seamlessly clinical activities and research, and has helped consolidate the role of research in pathology training. He has made mandatory the involvement of the pathology residents in research and has supervised more than 45 residents in molecular pathology and biomarkers-oriented research. He has been active in connecting research teams in different research centers and universities to create synergistic collaborations, especially in melanoma which is his main expertise. He also acts in different research consortiums, such as the Exactis NCE, which is a pan-Canadian research group on precision medicine. One of his recent initiatives, COSMET, is a consortium involving Quebec teams at McGill and Université de Montréal and partners from China that has received funding from FRQS. His research lab has two focuses: the molecular mechanisms associated with resistance to therapy, and the specific mechanisms of X chromosome inactivation and its relation to cancer. His lab has deciphered the role of the PPP2R3B protein in melanoma progression and its main partners, and has demonstrated the functional role of the gender-related haploinsufficiency. His research is also oriented towards the role of the interaction between CTCF and BORIS using X chromosome inactivation as a model of chromatin remodeling.

He has authored more than 190 original scientific papers, reports, review articles, and books.

Panel for Discussion

Janet Dancey (Panel & Session Co-Chair)

Dr. Dancey is Director, Canadian Cancer Trials Group (CCTG) and Scientific Director of the Canadian Cancer Clinical Trials Network (3CTN) and Senior Investigator, Melanoma Disease Site Committee for CCTG, and Professor, Department of Oncology, Queen's University. Previously, she was Program Leader for High Impact Clinical Trials, Ontario Institute for Cancer Research, Director, Clinical Translational Research and Chair, Cancer Care Ontario Experimental Therapeutics Network. From 1999-2008, she as senior investigator and rose to Associate Chief in the Investigational Drug Branch of the Cancer Therapy Evaluation Program of the National Cancer Institute, United States. She completed medical school at the University of Ottawa in 1988. She received certifications in internal medicine and medical oncology from the Royal College of Physicians and Surgeons of Canada in 1992 and 1993 respectively. She has completed research fellowships at the CCTG (Formerly the NCIC Clinical Trials Group NCIC CTG) and at the Institut Gustave Roussy, Villejuif, France.

In her current position, Dr. Dancey is responsible for the strategic development and operational oversight of programs within CCTG and 3CTN. Her clinical focus is on melanoma and gastrointestinal malignancies. Key accomplishments included the development and implementation of the CCTG strategic plan, establishment of the High Impact Clinical Trial Program following successful international peer review, and the development of novel trials to evaluate investigational drugs in rare tumour settings, to evaluate next- generation sequencing technologies in cancer patient management. As Leader of the 3CTN, she is responsible that the network member trial staff and institutions have resources to rapidly initiate and conduct cancer clinical trials including those with complex biospecimen and imaging collections.

Dr. Dancey has expertise in methodologies related to the development, implementation and analysis of phase I, II, and III studies of cancer therapeutics and in the measurement of quality of life in cancer trials. She has been a co-investigator, principal investigator and study chair of institutional, industry, and Canadian cooperative group phase 1 and 2 trials. She was the co-applicant on one peer reviewed and three industry sponsored research grants.

Dr. Dancey has presented at national and international oncology meetings and has been an invited speaker at other cancer centres and CME events. She is a member of the Editorial Board of PDQ. She is/has been an ad hoc reviewer for peer reviewed journals such as the Lancet, Journal of Clinical Oncology, Journal of the National Cancer Institute, Proceedings of the National Academy of Science (USA), Clinical Cancer Research, Cancer Research, Cancer Chemotherapy and Pharmacology, Cell Differentiation and Bone Marrow Transplantation. She has been a member of the CCTG Investigational New Drugs Committee, CCTG Quality of Life Committee, CCTG Quality Assurance Committee, and CCTG GI Site Group, Colorectal Cancer Working Group. Dr. Dancey has been the recipient of awards for excellence in post-graduate teaching from the University of Toronto Department of Medicine (1994) and Division of Medical Oncology (1997, 1998).

Raffi Tonikian, Merck Canada

Raffi Tonikian is Associate Director Oncology Medical Affairs for Biomarkers, Melanoma and Breast Cancer at Merck Canada Inc, where he provides subject matter expertise and coordinates Medical Affairs activities. In addition, Dr. Tonikian is responsible for external collaborations and partnerships in the areas of basic and translational oncology research.

Prior to joining Merck Canada, Dr. Tonikian was Medical Advisor in Neuroscience at Novartis Pharmaceuticals Canada, where he supported Medical Affairs and clinical activities in the fields of Multiple Sclerosis and Neuromuscular diseases.

Dr. Tonikian was a Scientist in the Departments of Protein Engineering and Translational Medicine at Biogen in Cambridge, Massachusetts. His work focused on the screening of antibody libraries for the discovery of antibody-based therapeutics for autoimmune disorders. In addition, he studied the utilization of T-cell repertoire diversity assessed using next-generation sequencing as a potential biomarker for disease activity in autoimmunity.

Raffi received his doctorate degree from the University of Toronto in the Department of Molecular Genetics, where he used peptide phage display libraries to identify specificity profiles for signaling domains, which led to the mapping of large-scale protein interaction networks in several model organisms. During that time, he also spent nearly two years at Genentech, Inc. as a Visiting Scientist in the Department of Protein Engineering. Dr. Tonikian performed his postdoctoral work at the Centre for Cellular and Biomolecular Research in Toronto, where he developed and utilized phage-displayed libraries to isolate antibodies against cancer related antigens. In addition, he worked on the development of antibody-DNA conjugates as biomarker detection reagents

Selected CSPS Oral Abstract Presentation

Combining Statins with Radio-immunotherapy as a Novel Therapeutic Strategy for Colorectal Cancer

Vessie Vassileva, Imperial College London

(See Poster Abstract # 13)

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Thursday, May 24

SESSION 4B:

Cannabinoids

Chair: Rachel Tyndale, CAMH

Session Chair:
Rachel Tyndale
Rachel Tyndale PhD is head of Pharmacogenetics at the Campbell Family Mental Health Research Institute, Centre for Addiction and Mental Health, the Canada Research Chair in Pharmacogenomics, and a Professor in the Departments of Pharmacology & Toxicology, and Psychiatry at the University of Toronto. Dr. Tyndale focuses on sources of variation between individuals in drug response in the clinical area of addictions and mental health, with a focus on smoking and opioids. Dr. Tyndale seeks to identify and understand risk factors, and underlying mechanisms, in substance abuse and to implement approaches to personalize treatment. Her laboratory program also has a major interest in understanding how interindividual variation in drug metabolizing enzymes within the brain alters drug and toxin effects. Dr. Tyndale sits on numerous scientific advisory boards, editorial boards, was chair for NIH's PharmacoGenomics Research Network (PGRN.org), and is a lead writer for the 2018 Surgeon General's Report on Tobacco Cessation. Dr. Tyndale has supervised over 100 scientists, post-doctoral fellows and graduate students, published over 350 papers and book chapters, given over 250 invited presentations and received over 40 awards in clinical and basic pharmacology.

Therapeutic Potential of CB1 Allosteric Modulators

Catharine A. Mielnik[1], Vincent M Lam[1], Iain R. Greig[2], Ali Salahpour[1], Amy J. Ramsey[1], Ruth A. Ross[1], [1]University of Toronto, Faculty of Medicine, Department of Pharmacology & Toxicology; [2]University of Aberdeen, UK, institute of Medical Sciences

Activation of the endocannabinoid system is postulated to have opposing roles in various disorders; the effect being either 'autoprotective' (e.g. pain) or 'autoimpairing' (e.g. obesity, fatty liver disease). We have developed a portfolio of novel small molecules that target the allosteric binding site on the cannabinoid CB1 receptor; these include both positive allosteric modulators (PAMs) which we are testing in models of pain and negative allosteric modulators (NAMs) which we are testing models of fatty liver disease, biopolar disorder and schizophrenia. CB1 PAMs have been shown to be effective neuropathic pain models and demonstrate no evidence of psychoactive side effects seen with CB1 agonists. Furthermore they do not show tolerance on repeated administration.

There is a critical need for novel treatment approaches for psychiatric disorders. Perturbations in the dopaminergic system playing a role in a number of psychiatric disorders. Relating to the dopamine system, the endocannabinoid systems serves as an important filter of afferent inputs, helping shape how incoming information is conveyed onto dopamine neurons and to output targets. GluN1-knockdown (GluN1KD - F1: C57Bl/6J x 129S1/SvlmJ) and DAT-knockout (DATKO - C57Bl/6J) mice display hyperactivity, impaired habituation and sensorimotor gating, along with increased stereotypy and vertical activity, in a state of mania-like behaviour. Following acute treatment with the CB1 NAM, ABM300 (10mg/kg), amelioration of these dysregulated behaviours was observed. The data suggest that CB1NAMs represent a novel treatment for psychiatric symptoms as a result of dopamine dysregulation. Furthermore, targeting the endocannanbioid system offers the opportunity to normalize deficits that arise from differing underlying dysfunctions that manifest as similar behavioural changes; both of which are mediated by dopamine dysregulation.

Ruth A. Ross
Ruth Ross obtained a PhD in Pharmacology from The University of Edinburgh in 1990. She has held research positions at Pfizer and Allergan Inc. In 2008 Dr Ross became Chair in Molecular

Pharmacology at The University of Aberdeen in Scotland. In 2013, she relocated to The University of Toronto to take up the position of Chair of the Department of Pharmacology and Toxicology. Her research over the last 25 years has focussed on the molecular pharmacology of the endocannabinoids and phytocannabinoids. Her current research involves characterisation of novel small molecules that offer new avenues for drug discovery by targeting the endocannabinoid system and related orphan receptors for the treatment of pain, liver disease and mental health disorders. Her research is also focussed on the molecular pharmacology and biological targets of cannabis constituents with the goal of gaining a deeper understanding of both the potential deleterious and beneficial effects of cannabis.

Growing up High: Long-Term Consequence of Adolescent Cannabis Use - Preclinical Studies

Jibran Khokhar, Assistant Professor, Department of Biomedical Sciences, Ontario Veterinary College, University of Guelph, Guelph, ON

Adolescent cannabis use occurs commonly, affects neurodevelopment, and is a risk factor for schizophrenia, as well as future substance use. Schizophrenia, itself, is associated with high rates of alcohol and drug use as well as motivational and reward-learning dysfunctions. Thus we were interested in whether Δ9-tetrahydrocannabinol (THC) exposure during adolescence would influence reward related behaviors in adulthood, especially in the context of neurodevelopmental risk for schizophrenia. Using a neurodevelopmental model of schizophrenia, the neonatal ventral hippocampal lesioned (NVHL) rat, we assessed the effects of adolescent THC (or vehicle) treatments (post-natal day 28-42; 6 mg/kg i.p.) on: (a) free-access 2-bottle choice alcohol (20% v/v) drinking; (b) context-based instrumental food reward acquisition, extinction, renewal and reinstatement; and (c) limited access sweet-fat food binge-like eating (n=5/group). In a subsequent study, we assessed the effects of adolescent THC (or vehicle) treatment on the acquisition and extinction of Pavlovian autoshaping (sign-tracking) behavior (n=15-16/group). Neither NVHL-lesion status nor adolescent THC treatment altered free-access alcohol intake in adulthood. Adolescent THC treatment, however, significantly impaired the motivation to lever press for a food reward in both the NVHL and sham animals; both THC treated groups showed decreased responding throughout the entire acquisition period, consistent with decreased motivation to work for a reward in adolescent cannabis smokers. In contrast, only the THC-treated sham animals showed reduced food cup entries, while extinction or renewal of lever pressing did not differ between groups. Conversely, the NVHL animals displayed impaired reinstatement of lever-pressing if given food pellets in the extinction context. Lastly, THC-treated NVHL and sham animals displayed decreased binge-like sweet-fat food consumption in a limited-access paradigm. In the autoshaping study, adolescent THC treatment significantly increased sign-tracking compared to vehicle treatment (consistent with increased cue-reactivity in adolescent cannabis smokers). This study suggests the adolescent THC exposure may produce long-term changes in reward-related behaviors, independent of risk for schizophrenia. The discordant findings between instrumental and Pavlovian conditioning may also provide important clues regarding the neurobiological and behavioral underpinnings of the potential “gateway drug” effects of adolescent cannabis use as it relates to the risk for future substance use.

Jibran Khokhar

Dr. Khokhar completed his undergraduate training at Queen’s University, and his Ph.D. in the Department of Pharmacology and Toxicology at the University of Toronto, under the supervision of Dr. Rachel Tyndale. During this time, Dr. Khokhar was awarded a CIHR Tobacco Use in Special Populations Fellowship, as well as a publication award for "Best Publication in Neuropsychopharmacology." He then completed a post-doctoral fellowship in the Department of Psychiatry at Dartmouth College with Dr. Alan Green. In addition to numerous travel and poster awards, Dr. Khokhar held a CIHR Post-doctoral Fellowship as well as NIH K99/R00 Pathway to Independence Award from the National Institute on Alcohol Abuse and Alcoholism. Dr. Khokhar was recently hired as an Assistant Professor in the Biomedical Sciences Department at the University of Guelph. Dr. Khokhar’s research aims to understand the mechanisms underlying co-occurring schizophrenia and substance use disorders, using a variety of behavioural, pharmacological and translational neuroimaging techniques. In addition, his research interests also include assessing the long-term effects of adolescent drug (e.g., cannabis) use,

and how these effects might contribute to the risk for serious mental illness and addiction.
Website: https://ovc.uoguelph.ca/biomedical-sciences/people/faculty/Jibran-Khokhar

Adolescent Cannabis Use: Risk for Mental Health and Drug Dependence

Marcus Munafò, Professor of Biological Psychology, School of Experimental Psychology, University of Bristol

Cannabis use is strongly associated with subsequent adverse mental health outcomes and dependence on other substances, but determining whether or not this reflects a causal effect of cannabis use is complex. Well-established problems of residual confounding and reverse causality mean that strong causal inference is impossible in conventional epidemiology. Mendelian randomization is a form of instrumental variable analysis that uses genetic variants associated with exposures of interest (e.g. cannabis use) to leverage stronger causal inference. This method has grown rapidly in popularity as an increasing number of relevant genetic variants have been identified via genome-wide association studies. Using this approach, we have shown that cannabis use increases subsequent risk of schizophrenia, but also that genetic risk of schizophrenia increases the likelihood of cannabis use initiation. This suggests that some of the observational association between cannabis use and schizophrenia may in fact be due to reverse causality (e.g. self-medication through the use of cannabis). We have also shown that tobacco use, which is extremely common among regular cannabis users, is also likely to be a causal risk factor for schizophrenia (but, in this case, that schizophrenia risk does not lead to tobacco use). We have also shown that tobacco use leads to subsequent cannabis use, but not vice versa. Therefore, while adolescent cannabis use does appear to be a causal risk factor for schizophrenia, tobacco use also appears to play an important role.

Marcus Munafò
Marcus Munafò is Professor of Biological Psychology in the School of Experimental Psychology at the University of Bristol, and Director of the Tobacco and Alcohol Research Group (http://www.bristol.ac.uk/expsych/research/brain/targ/). His group is part of the UK Centre for Tobacco and Alcohol Studies, and the Medical Research Council Integrative Epidemiology Unit at the University of Bristol. He was an undergraduate at the University of Oxford, before moving to the University of Southampton to complete an MSc in Health Psychology and a PhD. Following this, he returned to the University of Oxford, as a postdoctoral fellow in the Department of Public Health and Primary Care and later the Department of Clinical Pharmacology. In 2004-2005 he spent 6 months as a Visiting Professor at the University of Pennsylvania. In March 2005 took up a tenured position at the University of Bristol. He was promoted to Reader in Biological Psychology in 2008, and Professor of Biological Psychology in 2010.

Professor Munafò's research focuses on understanding pathways into, and the consequences of, health behaviours and mental health, with a particular focus on tobacco and alcohol use. This work incudes: 1) observational and genetic epidemiology, and the use of a range of methods that enable stronger causal inference from observational data, such as negative control and Mendelian randomization methods; 2) the laboratory study of cognitive and neurobiological mechanistic pathways that underpin exposure-outcome relationships; and 3) the development of novel individual- and population-level interventions that target these mechanisms, including choice architecture interventions. This work has informed ongoing policy debates, such as the introduction of standardised ("plain") packaging for tobacco products. He also has interests in the role of incentive structures in science, and the extent to which these shape the robustness and reproducibility of scientific research.

Opioid Sparing Effects of Cannabinoids: Myth or Reality?

Bernard Le Foll, Medical Head, CAMH; Professor University of Toronto

Cannabinoids, when co-administered with opioids, may enable reduced opioid doses without loss of analgesic efficacy (ie, an opioid-sparing effect). This presentation will focus on presenting the results of a systematic review to determine the opioid-sparing potential of cannabinoids. Eligible studies included pre-clinical and clinical studies for which the outcome was either analgesia or opioid dose requirements. Clinical studies included controlled

studies and case series. We searched Scopus, Cochrane Database of Systematic Reviews, Medline, and Embase. Nineteen pre-clinical and nine clinical studies met the search criteria. Seventeen of the 19 pre-clinical studies provided evidence of synergistic effects from opioid and cannabinoid co-administration. Our meta-analysis of pre-clinical studies indicated that the median effective dose (ED_{50}) of morphine administered in combination with delta-9-tetrahydrocannabinol (delta-9-THC) is 3.6 times lower (95% confidence interval (CI) 1.95, 6.76; n=6) than the ED_{50} of morphine alone. In addition, the ED_{50} for codeine administered in combination with delta-9-THC was 9.5 times lower (95% CI 1.6, 57.5, n=2) than the ED_{50} of codeine alone. One case series (n=3) provided very-low-quality evidence of a reduction in opioid requirements with cannabinoid co-administration. Larger controlled clinical studies showed some clinical benefits of cannabinoids; however, opioid dose changes were rarely reported and mixed findings were observed for analgesia. In summary, pre-clinical studies provide robust evidence of the opioid-sparing effect of cannabinoids, whereas one of the nine clinical studies identified provided very-low-quality evidence of such an effect. Prospective high-quality-controlled clinical trials are required to determine the opioid-sparing effect of cannabinoids. Those findings will be discussed along more recent findings and put into perspective on how those systems may interact.

Bernard Le Foll

Dr. Bernard Le Foll, MD PhD MCFP is a clinician-scientist specialized in drug addiction. He is the Medical Head of the Concurrent Outpatient Medical & Psychosocial Addiction Support Service at the Centre for Addiction and Mental Health (CAMH), providing care to several thousands of patients per year through a multi-disciplinary clinical team. He is the Head of the Translational Addiction Research Laboratory within the Campbell Family Mental Health Research Institute of CAMH and Head of the Alcohol Research and Treatment Clinic within CAMH. He is a Professor at University of Toronto in the Departments of Family and Community Medicine, Psychiatry, Pharmacology and Institute of Medical Sciences and holds several graduate faculty appointments. Dr Le Foll has published >160 peer-reviews manuscripts, H-index 46, >6,000 citations. He has performed research on the treatment of cannabis use disorders, impact of cannabis of driving and the medical use of cannabis. He has received numerous awards and his research is funded by CIHR, NIH and other funding agencies. He has been consultant/advisor for CAMH, CCSA, NIH and Health Canada and has presented on cannabis issue to the House of Commons and to the Senate. He has contributed to the CAMH cannabis policy statement and to the development of Lower Risk Cannabis Use Guidelines.

Panel Discussion:

The Future of Medical Cannabis in Canada

Co-Chairs: Christine Allen, University of Toronto, and Aras Azadian, Avicanna

PANEL MEMBERS

Avicanna: Aras Azadian, President

Aras is the chief executive officer and a co-founder of Avicanna, and brings with him extensive senior management experience in the biotechnology and financial sectors including his involvement in several successful start-ups. In addition to his international experience in corporate development his diverse roles included his position as the president of an investment corporation in the cannabis space and former COO of an oncology company. Aras has degree in economics from York University in Toronto and MBA from EADA Business School in Barcelona.

Beleave: Peter Chen, Vice President of Science and Technology

Dr. Peter Chen holds a PhD in food science from the University of Guelph and Agriculture and Agri-Food Canada and is the recipient of the 2017 Governor

General's Academic Gold Medal for academic excellence. His research at the University of Waterloo – School of Pharmacy and the University of Guelph – Department of Food Science is funded through NSERC and Beleave Kannabis Corp. As Vice-President of Science & Technology at Beleave, his focus is on developing novel drug delivery systems for cannabinoids and to assess their pharmaceutical application potentials such as bioavailability using a state-of-the-art simulated *in vitro* gastrointestinal digestion system.

CannTrust: Kaivan Talachian, Vice President, Professional Services

Kaivan Talachian holds a doctorate in pharmacy (Pharm. D) and is a practicing pharmacist in Canada with more than 20 years of diverse experience in pharmaceutical, medical device and healthcare information technology.

He has been involved in the medical cannabis research, education and innovation since 2013. He is currently the vice president of healthcare services at CannTrust, a publicly traded licensed producer of medical cannabis. He has directed the transformation of this business from a startup to a billion-dollar business. He is directing the development of innovative cannabinoid dosage forms, clinical education programs and cannabinoid based clinical trials.

Prior to CannTrust, Kaivan was the vice president of healthcare products at NexJ Systems, a publicly traded Canadian company. In this role he directed development and design of a patient-centric software solution to activate and educate patients, collaborate care and improve medication adherence. This solution is being used by Prostate Cancer Canada.

Kaivan has held senior positions at Baxter Pharmaceuticals and major pharmacy groups, such as Shoppers Drug Mart, Loblaw pharmacy and Costco Pharmacy. He has trained many pharmacists and pharmacy technicians and has been a member of the peer review panel at Hospital Pharmacy Journal.

University of Toronto: Lakshmi P. Kotra, B. Pharm.(Hons), Ph.D.

Dr. Kotra is Professor, Leslie Dan Faculty of Pharmacy, University of Toronto; Senior Scientist, Toronto General Hospital Research Institute and Multi-Organ Transplant Program, and Director, Center for Molecular Design and Preformulations, University Health Network, Toronto (Canada)

Dr. Kotra is an academic entrepreneur with expertise in drug discovery and development (http://kotralab.uhnres.utoronto.ca/). Kotra group specializes in the areas of medicinal chemistry, preclinical and clinical development of small molecule and natural product-based drugs. Dr. Kotra authored/co-authored over 120 peer-reviewed articles and book chapters, and delivered over 110 scientific and plenary talks globally. Kotra research group has contributed to a number of research programs in the areas of infectious, metabolic and neurodegenerative diseases. Dr. Kotra is a recipient of several awards including the Premier's Research Excellence Award from the Province of Ontario (Canada), Rx&D Health Research Foundation Research Career award, GlaxoSmithKline/Canadian Society for Pharmaceutical Sciences Young Investigator Award. Dr. Kotra leads an international consortium with India for the development of novel chemical classes of drugs targeting malaria—a consortium of public and private organizations in Canada and India. Dr. Kotra is a co-founder of WinSanTor Inc., San Diego, California, USA (drugs targeting diabetic neuropathy, 2012-present), CIDAVA Innovations—an India-Canada joint venture (antimalarials, 2013-17), CannScience Innovations, Inc., Toronto, Canada (now Scientus Pharma, Inc.; novel cannabinoid products for medical uses, 2014-17). He currently serves on the Board of Directors of WinSanTor Biosciences (San Diego, CA), Scientific Advisory Boards of Scientus Pharma Inc. (Toronto) where he maintains Chief Scientific Officer role, Montdorex Inc. (Montreal, Canada), and College of Reviewers at the Canadian Institutes of Health Research. Dr. Kotra lives in Toronto with his wife, Dasantila and their two daughters, Radha and Geetha.

Thursday, May 24

SESSION 4C:

Innovative Biomaterials for Drug Delivery

Co-Chairs: Todd Hoare, McMaster University, Marta Cerruti, McGill University

Trigger-Amplifying Self-Immolative Nanoparticles for Drug Delivery

Elizabeth Gillies, Department of Chemistry, Department of Chemical and Biochemical Engineering, The University of Western Ontario, London, Canada

Degradable polymers are of significant interest in nanomedicine, where they are frequently used to prepare nanoparticles that can encapsulate drugs and then release them as the polymers break down. Much progress has been made using polyesters such as polylactide and polycaprolactone. However, the ability to control drug release using these polymers is limited as they may degrade more rapidly or more slowly than desired. Many stimuli-responsive polymers have been developed over the past couple of decades, but these polymers typically require many stimuli-mediated events to achieve complete polymer degradation. To address these limitations, we have been developing self-immolative polymers (SIPs), which undergo complete end-to-end depolymerization following the cleavage of a single stimuli-responsive end-cap from the polymer terminus. This presentation will describe our group's development of polyglyoxylate SIPs and their applications in nanomedicine. We have prepared polyglyoxylates with end-caps responsive to a wide range of stimuli including light, heat, weak acids, hydrogen peroxide, and reducing agents, many of which are accessible *in vivo* and are associated with disease states such as cancer and inflammation. Their degradation was studied in solution, as assemblies of block copolymers, in the form of nanoparticles, and as coatings. In each case, the triggered polymers underwent rapid depolymerization whereas the untriggered controls remained quite stable. This provided triggered release of drug molecules. The toxicity of the delivery system was also investigated *in vivo.* Overall, these studies have demonstrated that polyglyoxylates have great potential for drug delivery applications.

Elizabeth Gillies
Elizabeth Gillies is a Professor in the Department of Chemistry and Department of Chemical and Biochemical Engineering at the University of Western Ontario. She received her PhD in Chemistry at the University of California, Berkeley with Jean Fréchet, then was a Marie Curie Postdoctoral Fellow at the European Institute of Chemistry and Biology in Bordeaux with Ivan Huc. Her research group focuses on the development of new biodegradable, multifunctional, and stimuli-responsive polymers as well as their applications in drug delivery and other biomedical areas. She has received a number of awards including a Canada Research Chair, NSERC E. W. R Steacie Memorial Fellowship, and an Early Researcher Award.

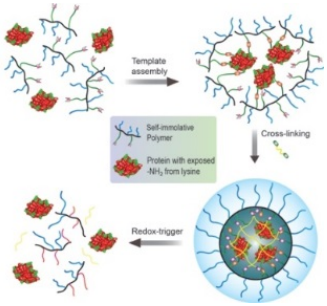
Polymer-Based Protein Delivery Systems

S. Thayumanavan, Department of Chemistry, University of Massachusetts, Amherst, MA
Email: thai@chem.umass.edu

Using proteins as a therapeutic is attractive, as this promises to directly address genetic deficiencies and therefore mitigates side-effects that plague many small molecule drugs. Potential side-effects from small molecule binders are understandable, as these molecules must be designed to target a specific protein in our complex biological system, highlighted by the nearly 20,000 protein-encoding genes. On the other hand, proteins can directly compensate for a specific deficiency and therefore the drug development is less heuristic. However, realizing the full potential of protein-based therapeutics has been difficult, mainly due to their in vivo instability and immunogenicity. To overcome these issues, approaches to modify protein surfaces have been taken. These reports provide examples of

innovative strategies that allow for enhanced circulation lifetimes and thus have impacted the utility of proteins that function in the extracellular environment.

The next significant challenge would involve development of systems for intracellular proteins, where trafficking the biomolecule across a cellular membrane is a hurdle. Two limiting approaches, involving electrostatic interactions or liposomal encapsulation, have been taken to address this need, Non-specific fouling of the complex' surfaces due to electrostatic interactions and low loading capacities in liposomes, along with the lack of triggerability, have limited the reach of these approaches. We will present a novel covalent self-assembly approach, where the protein cargo itself acts as the template for the polymer to self-assemble around it, has the potential to encapsulate proteins with high fidelity and present charge-neutral surface functionalities.



Covalent polymer network formation using the protein as the template

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S. "Thai" Thayumanavan

S. "Thai" Thayumanavan is a Professor in the Department of Chemistry at the University of Massachusetts Amherst. He received his B.Sc. and M.Sc. degrees from The American College in Madurai, India. He received his Ph.D. from the University of Illinois at Urbana-Champaign in 1996. Following a postdoctoral stint at Caltech, he started his independent career at Tulane University in 1999 and moved to UMass Amherst in 2003. His research work involves the design and syntheses of new macromolecules, especially polymers, to obtain novel responsive supramolecular nanoassemblies. These responsive nanoassemblies are being pursued for applications in the delivery of small molecules and biologics, in addition to imaging and diagnostics applications. His work has resulted in more than 200 peer-reviewed publications in high-impact journals. The innovation in his work has also produced about 15 patents and patent applications. Thai has received numerous national and international recognitions for his creative contributions. Thai is the scientific founder of a start-up company Cyta Therapeutics, which is focused on translating a versatile polymeric nanogel platform to the clinic.

Controlled-Release Nano-Therapeutics: The Status of Translation

Subbu Venkatraman, School of Materials Science and Engineering, Nanyang Technological University; Singapore. E-mail: assubbu@ntu.edu.sg

Although pharmaceutical products based on controlled-release of the drug are commonplace now, such products typically employ macro- and micro-sized carriers. Doxil® was the first nanoliposome-based delivery system that won approval in 1995, and this system is able to control the release of doxorubicin for a few days. Subsequent research into nanocarriers has focused largely on oncology with varying degrees of success. It is fair to say that Nanomedicine administered systemically will have limited duration of action, due to clearance mechanisms. Therefore, our focus on controlled-release nanotherapeutics has been on locally-administered concepts.

We present two case studies of controlled-release in the treatment of ocular disease. The first involves the control of intra-ocular pressure, an indicator of glaucoma, over several days with a single sub-conjuctival injection. The system here is a nanoliposome which incorporates the drug, latanoprost, in its lipid bilayer. If only diffusion were to control the release, this system would exhaust its payload within a few hours (the bilayer is

only about 5-10 nm thick). In contrast to Doxil, we show that this system is able to control the release of the drug over 45-60 days under sink conditions. We attribute this control to partitioning effects, based on isothermal calorimetric studies of drug-lipid interactions[2].

However, for the sustained delivery of gene silencing molecules, which are hydrophilic in general, and of larger size, nanoliposomes are poor carrier candidates. For this we developed a polyelectrolyte layer-by-layer (LbL) approach to sustain the release of siRNA, which forms one or more of the layers. We developed this system using a hydroxyl apatite nanoparticle core, and optimized the polycationic layer using poly (L-arginine) [3]. With this system, we employed a sub-conjuctival injection to treat fibrosis in a glaucoma filtration surgery model and showed that the fibrosis could be suppressed over 14 days with a single injection.

Controlled release from nanoparticles is not as easy to achieve as with microparticles. Nevertheless, we show that for lipophilic molecules, we can sustain in vitro delivery for over 30 days with selected liposomal compositions using partitioning; whereas for siRNA delivery, we have employed a layer-by-layer system that release the siRNA via slow defoliation.

Subbu Venkatraman

Professor Subbu Venkatraman has a PhD in Polymer Chemistry from Carnegie-Mellon University. He has spent about 15 years in biomedical R&D in the USA, working with various applications of polymeric biomaterials. He held a senior position in R&D at Alza Corporation (now Johnson & Johnson) prior to joining NTU as Associate Professor in 2000. Since then he has published extensively in the field of biomaterials, with a total of 225 publications, H-index of 35 and a citation count of 5160 He also holds 88 granted patents from a total of 171 applications. His work in biomaterials has led to 3 successful spin-off companies, with one of them (Amaranth Medical) obtaining substantial series C funding. He has also received the 2014 President's Technology Award together with Prof Freddy Boey and Adjunct A/P Tina Wong, for their innovative application of nanostructures and novel drug delivery approach to combat blindness from glaucoma. He is also the co-founder of Peregrine Ophthlamic Pte Ltd and Amaranth Medical Pte Ltd.

His research group is interested in designing and modifying materials for biomedical applications. In this work, they are closely associated with local hospitals and researchers, including the National Heart Centre, Tan Tock Seng Hospital and the National Cancer Centre. Current interests include the following: Nanomedicine, Localized drug/gene delivery, Biodegradable polymers, Injectable implants and nanoparticles, Bio-inspired solutions to medical problems.

Biomimetic Nanoparticles for Targeted Drug Delivery and Detoxification

Liangfang Zhang, Professor, Department of Nanoengineering and Moores Cancer Center, University of California San Diego

The emerging nanotechnology in biomedicine has sparked new hope for the treatment and diagnosis of various important human diseases. However, development of functional nanomaterials and nanodevices can be encumbered by unanticipated material properties and biological events, which can negatively impact their effectiveness when introduced into complex, physiologically relevant systems. In this talk the preparation of nanoparticles enclosed in the plasma membrane of natural human cells (e.g., RBCs, platelets, cancer cells, etc) is reported. The resulting cell membrane-coated nanoparticles are demonstrated to possess many surface functions of natural cells via studies of interactions with plasma proteins, cells, tissues, and microorganisms. Such multifaceted cell-mimicking properties can be attributed to the preservation of biomembrane on nanoparticle surfaces, which facilitates the display of intricate biochemistry that is difficult to replicate using conventional functionalization approaches. As the platform is entirely biocompatible and biodegradable, it can be applied toward a myriad of biomedical applications, including active drug delivery and detoxification, where the vast implications of cell surface properties may benefit a variety of disease treatments.

Liangfang Zhang

Dr. Liangfang Zhang received his B.E. and M.S. degrees in Chemical Engineering from Tsinghua University, and his Ph.D. in Chemical & Biomolecular Engineering from the University of Illinois at Urbana-Champaign in 2006 under the supervision of Prof. Steve Granick. He was a postdoctoral associate in the laboratory of Prof. Robert Langer at MIT during 2006-2008. He joined the Department of Nanoengineering at UC San

Diego as an Assistant Professor in July 2008 and was promoted to an Associate Professor with tenure in March 2012 and to Professor in July 2014. Dr. Zhang's research interests focus on biomimetic nanomedicine, with a particular interest in creating and evaluating nanostructured biomaterials for drug delivery, detoxification and vaccination for treatment of infectious diseases and cancer. He has published 165 peer-reviewed articles and holds 55 issued/pending patents. He received the ACS Victor K. LaMer Award (2009), UCSD Jacobs School of Engineering Best Teacher Award (2011), ACS Unilever Award (2012), MIT Technology Review's TR35 Innovator Award (2013), AIChE Allan P. Colburn Award (2014), AIMBE Fellow (2015), Popular Science's Brilliant 10 Award (2016), U.S. Department of State ASPIRE Award (2017), and Kabiller Young Investigator Award (2017).
http://nano.ucsd.edu/~l7zhang/

Selected oral abstract presentation:

Hyperthermia-mediated Drug Delivery Increases Cisplatin Sensitivity and Accumulation Resulting in improved Efficacy in Triple Negative Breast Cancer

Michael Dunne, University of Toronto
(See Poster Abstract # 94)

Friday, May 25

PLENARY SESSION 4

Richard Weinshilboum, Mayo Clinic

Chair: Micheline Piquette-Miller, University of Toronto

Pharmacogenomics: Clinical Implementation and Future Challenges

Richard Weinshilboum, Professor of Pharmacology and Medicine and Dasburg Professor of Cancer Genomics Research, Mayo Clinic

Pharmacogenomics, the science of the role of inheritance in variation in drug response phenotypes, is almost certainly the aspect of clinical genomics that will eventually touch every patient everywhere. Pharmacogenomics continues to advance as discovery science and—at the same time—it is being translated and implemented in the Clinic. This presentation will outline challenges associated with Pharmacogenomic translation and clinical implementation. It will also outline some of the trends in pharmacogenomic discovery science, including the merging of multiple "omics" data types to become "Pharmac-omics".

Richard Weinshilboum
Dr. Weinshilboum received B.A. and M.D. degrees from the University of Kansas, followed by residency training in Internal Medicine at the Massachusetts General Hospital in Boston. He was also a Pharmacology Research Associate at the NIH in the laboratory of Nobel Laureate Dr. Julius Axelrod. He is presently Professor of Pharmacology and Medicine and Dasburg Professor of Cancer Genomics Research at Mayo Clinic. He also co-directs the Pharmacogenomics Program of the Mayo Center for Individualized Medicine. Dr. Weinshilboum's research has focused on pharmacogenetics, with over 425 manuscripts on that topic. His major area of research has been the pharmacogenetics of drug metabolism, with a focus on methylation and sulfation. He has also applied genome-wide "omics" to study drug response—especially the drug therapy of depression and breast cancer. Dr. Weinshilboum has been the recipient of many awards including an Established Investigatorship of the American Heart Association, a Burroughs Wellcome Scholar Award in Clinical Pharmacology, the Oscar B. Hunter Award of the American Society for Clinical Pharmacology and Therapeutics, the ASPET Harry Gold Award and the Edvard Poulsson Award from the Norwegian Pharmacology Society. He has also served on the Advisory Councils for two US NIH Institutes, the NIGMS and NHGRI.

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Friday, May 25

SESSION 5A:

Pharmacogenomic Implementation

Chair: Micheline Piquette-Miller, University of Toronto

Session Chair:
Micheline Piquette-Miller

Micheline Piquette-Miller is a Professor at the Leslie Dan Faculty of Pharmacy at the University of Toronto and an Associate Editor of Clinical Pharmacology & Therapeutics. Dr. Piquette-Miller completed a BSc. in Pharmacy and PhD in Pharmacokinetics at the University of Alberta and a Postdoctoral Fellowship at the University of California in San Francisco. Her research primarily focuses on understanding the regulation of drug transport proteins and how this impacts drug disposition. She has published over 100 research articles and has been the recipient of numerous prestigious national and international research awards including ASCPT's Leon Goldberg Young Investigator Award, RX&D/CIHR Research Career Award; Pfiasky Young Investigator Award, University of Alberta's Horizon Award, AFPC's Pfizer Research Career Award, FDA's ORISE Fellowship Award and Canadian Society of Pharmaceutical Sciences (CSPS) Fellow Award. She is currently Chair of ASCPT's International Transporter Community and has previously served on the executive councils of ASCPT and CSPS, and is a past-president of the Canadian Society of Pharmacology & Therapeutics (CSPT).

PRIME: Implementing Pharmacogenomic Testing into Pharmacy Practice - Focus on Mental Health Pharmacotherapy

Natalie Crown, Leslie Dan Faculty of Pharmacy, University of Toronto

Pharmacists are ideally positioned to lead the integration of pharmacogenomics into practice by partnering with patients and their prescribers to optimize medication therapy outcomes. The objectives of PRIME (Pharmacists as Personalized Medicine Experts in Primary Care) were: 1. to develop, implement and evaluate a pharmacogenomic specialization training program directed to pharmacists, and 2. to assess the use of pharmacogenomic testing initiated by pharmacists in primary care settings.

Methods: The pharmacist's training program was comprised of online lectures, a two-day training workshop, and completion of patient case pharmacotherapy work-ups. Pharmacists then recruited patients in their practice to receive the pharmacogenomics service. Eligible patients were aged > 18 years, were starting or switching to a new antidepressant or antipsychotic medication, demonstrated poor response or experienced significant and repeated side effects to these agents. Patients were followed up for 2 months post-testing. The study was conducted in collaboration with the CAMH IMPACT study.

Results: Twenty-two pharmacists successfully completed the training program, demonstrating improved knowledge and confidence in applying pharmacogenomics in practice. A total of 187 patients were invited to participate by 15 pharmacists (with a wide range in the number of patients included per pharmacist: 0 to 42 patients). Of these, 127 patients completed at least one study visit and 65 patients completed all visits. Most patients were female (60%), mean age 47±13 years (range 18-75 years). Many patients were new to the pharmacist and practice site (70%), although pharmacists reported established relationships with the prescribers for 91% of patients. Reasons for recommending pharmacogenomics testing were: poor response to an antidepressant (67%) or antipsychotic (6%), switching (32%) or starting (17%) a new antidepressant, and/or significant and repeated side effects to an antidepressant (24%) or antipsychotic (4%). Of the medication recommendations made by pharmacists at the post-testing results visit, most were for a medication

change (62%), a dose increase (10%) or a dose decrease (8%). By the end of the study 46% of those attending the final visit (n=29 of 65 patients, or 24% of all patients) had Clinical Global Impression (CGI) ratings indicating marked or moderate improvement with side effects either not present or not significantly interfering with functioning. Positive outcomes were also suggested with other included clinical measures.

Conclusion: Most pharmacists in PRIME were able to provide pharmacogenomics services in their primary care practice, working with patients and prescribers to improve medication outcomes. The reasons for testing were primarily related to problems associated with antidepressant therapy, with mostly medication change recommendations, and indications of positive clinical outcomes.

Natalie Crown

Natalie Crown is a Clinician Educator at Women's College Hospital and Assistant Professor with the Leslie Dan Faculty of Pharmacy at the University of Toronto. She completed her Bachelor of Science in Pharmacy at Dalhousie University, a pharmacy practice residency at Capital District Health Authority in Halifax NS, and her Doctor of Pharmacy degree at the University of Toronto.

She is a co-investigator in the research study "Pharmacists as Personalized Medicine Experts in Primary Care (PRIME)". For PRIME, she led the development a pharmacogenomics (PGx) specialization training program directed to pharmacists that could be adapted for other health professions. Dr. Crown was one of the first pharmacists in Canada to use pharmacogenetics in practice. She worked as part of a team with the Division of Clinical Pharmacology at Western University and London Health Sciences Centre to develop a personalized medicine warfarin clinic– the first of its kind in Canada. At Women's College Hospital she developed and serves as the Director of a Pharmacy Residency Program in ambulatory care, and maintains a practice in ambulatory care clinics.

Clinical Pharmacogenomics Program in Pediatric Oncology: 257 Patients and Counting

Bruce Carleton, PharmD, FISPE, Professor and Chair, Division of Translational Therapeutics, Department of Pediatrics, Faculty of Medicine, University of British Columbia; Senior Clinician Scientist, BC Children's Hospital Research Institute; Director, Pharmaceutical Outcomes Programme, BC Children's Hospital, Vancouver, BC

Adverse Drug Reactions (ADRs) cause significant morbidity and mortality. We built a national network in Canada (The Canadian Pharmacogenomics Network for Drug Safety or CPNDS) to rigorously characterize drug outcomes in children and in particular to find genomic solutions to the lack of predictability of many severe ADRs. Drug biotransformation and other genes are analyzed to determine their role in the development of specific ADRs and to identify predictive, clinically-relevant (odds ratios ≥3) genomic markers. Identified biomarkers are replicated and then validated with functional and pharmacokinetic studies. The identification of highly-predictive genomic markers is essential for developing diagnostic tests to predict which patients are at higher risk of developing ADRs so that patients, families and clinicians can make more informed decisions about the likelihood of therapeutic success and harm. We have now implemented pharmacogenomic testing in British Columbia for children undergoing cancer chemotherapy. All patients are tested. This session will highlight examples of the impact of pharmacogenomic testing on clinical decision-making, some of the key challenges in implementation, and next steps as CPNDS rolls out its pharmacogenomic implementation program in pediatric oncology across Canada.

Bruce C. Carleton

Dr. Carleton's lifelong goal is to make medication use more effective and safer for all patients, particularly children. His research focus is on the impact of drug therapy on human health and quality of life. He is particularly interested in developing better ways to evaluate the effectiveness of drugs, medication-use models designed to improve patient health, as well as practical surveillance systems to improve the safe use of medication.

A key element of Dr. Carleton's research is the communication of results to clinicians, patients, healthcare administrators, and government officials

– those who also hold responsibilities to improve patient care and our systems of healthcare delivery.

In addition to his appointment as Professor of Paediatrics and Chair of the Division of Translational Therapeutics, Department of Pediatric Medicine at UBC, Dr. Carleton is a Senior Clinician Scientist at BC Children's Hospital Research Institute. He directs the Pharmaceutical Outcomes Programme at BC Children's Hospital and he has served in this capacity since 1994. He holds appointments at UBC in the Centre for Health Services and Policy Research, the School of Population & Public Health and the Faculty of Pharmaceutical Sciences and the School of Health Information Science, University of Victoria. Dr. Carleton's public service is expansive. It includes serving as a charter member on the national Canadian Expert Drug Advisory Committee. Dr. Carleton was recently asked to serve the US Government as a Special Government Employee to advise the Advisory Committee for Pharmaceuticals and Clinical Pharmacology of the FDA.

Clinical Utilization of Pharmacogenomic Testing – The Evolving Canadian Environment

Christopher Trevors, MS, CGC National Director, Genetic Health Solutions, Dynacare

Pharmacogenomic testing has been used in medical research and limited segments of clinical care for decades, however, uptake more broadly has been slow. This talk will review briefly, the historic and current utilization of pharmacogenomics in Canada as well as future trends. Pharmacogenomic uptake, like many other beneficial genetic technologies, has been limited by structural limitations in the healthcare system, medical culture and cost. Despite all of the barriers there is a trend towards widespread utilization of pharmacogenomics within both the public and private healthcare environments in Canada. This increase is supported by a number of factors - improved computing power, decreased costs of laboratory analysis, positive medical, scientific and health economic publications, the rising costs of therapeutics, increasing absenteeism of employees as well as a broader awareness of health technologies. This demand is coming from consumers, clinicians, employers and insurance companies. Canada can and is playing a significant leadership role in improving our understanding of pharmacogenomics and personalized medicine. Pharmacists will play an integral role in supporting safe and responsible utilization of this technology as well as helping maximize its benefits to patients and the healthcare system.

Christopher Trevors

Christopher Trevors, MS, CGC graduated with a B.Sc. (Honours) in Biology from Queen's University and a master's degree in Human Genetics (Genetic Counseling) from Sarah Lawrence College in Bronxville, New York. He worked at the Westchester Medical Center in Hawthorne, New York before starting at The Hospital for Sick Children (SickKids) in Toronto as a genetic counsellor. During his nine years at SickKids he was involved in clinical care before taking on a role as a clinical educator and evaluator in the areas of genetics, ethics and molecular/genomic technologies. Christopher worked as Canadian General Manager of Centogene AG, a German molecular diagnostics company for 3 years before transitioning to help build a genetic diagnostics division at LifeLabs in Toronto as Director of Genetics and Genomics. Christopher is currently the National Director of Genetic Health Solutions at Dynacare where he is part of the business development team working to promote the utilization of genetic technologies across all business segments. He is a Lecturer in the University of Toronto Genetic Counselling MSc program, the Medical Laboratory Technology Program at The Michener Institute and the George Brown Nursing Program.

Pharmacogenetics in the Benefits Arena – Baby Steps; Giant Opportunities

Wayne Murphy, Prudent Benefits Administration Services Inc.

As we enter the age of Personalized Medicine, Pharmacogenetics is poised to provide consumers, prescribers and payers of drug benefits with a far safer, more customized and cost-effective approach to prescription for a wide range of drugs. Given the current landscape where there are more than 200,000 documented adverse drug reactions each year in Canada, some of those involving death AND where approximately 65% of mental health drugs prescribed are abandoned due to such causes as "side effects"; is it possible that pharmacogenetics could be a revolutionary advancement that will change the

world of pharmacology? This session will involve the sharing of an example of early adoption of pharmacogenetic testing in the Benefits arena. The speaker will tell his story of how his firm has used pharmacogenetic testing and anecdotally, what the impact and outcome looked like. The session will be an informal sharing as the case example represents baby steps in the areas of Disability Management and a unique Employer benefits program. The speaker will also undertake to share some of his impressions and conjecture around the barriers to utilization in the benefits arena.

Wayne Murphy

Wayne Murphy is the Senior Manager, Corporate Services and Chief Privacy Officer for Prudent Benefits Administration Services Inc. (The PBAS Group). The firm, founded in 1987, with seven offices across Canada, provides administration, actuarial and consulting services to plan sponsors across Canada. Murphy received his Certified Employee Benefits Specialist (CEBS) designation from Dalhousie University in 2004 and has been involved with the International Society of Certified Employee Benefits Specialists (ISCEBS) as a speaker and moderator. He also holds Fellowship status with the ISCEBS. In 2009, he was elected President of the Toronto Chapter, ISCEBS and, in 2014, was elected, National President of the ISCEBS. Most recently he was appointed Chair of the CEBS Committee for 2018 and will lead a Committee which will oversee the implementation of polices, plans, and procedures for the growth and development of the CEBS program with the International Foundation of Employee Benefit Plans (IF) which cosponsors the CEBS program with the Wharton School of the University of Pennsylvania and Dalhousie University.

Friday, May 25

SESSION 5B:

Drug Therapy in Children

Chair: Michael Rieder, Western University

Nephrotoxic Acute Kidney Injury in Hospitalized Children and Description of a National Cisplatin Pediatric Cohort

Mike Zappitelli, The Hospital for Sick Children, Toronto

[Abstract not available]

Mike Zappitelli

Dr. Zappitelli performs research on acute kidney injury (AKI) in children as well as measurement of pediatric blood pressure and kidney function. AKI mostly occurs in hospitalized patients. Research from Dr. Zappitelli's lab and others has shown that AKI in children is associated with hospital morbidity and mortality. Currently, the Zappitelli Lab is performing multiple studies in different patient populations (including cardiac surgery, critical illness and cancer treatment) to determine whether AKI causes long-term kidney damage and high blood pressure. This work is important, since chronic kidney damage (or chronic kidney disease) are important cardiovascular risk factors. The Zappitelli Lab is also trying to improve how AKI is diagnosed in hospitalized children, by studying new urine and blood biomarkers of AKI, specifically for early AKI diagnosis. Part of studying long-term kidney outcomes of AKI, includes trying to determine the best way to measure kidney function and express blood pressure in children. Thus, the second major aspect of the Zappitelli Lab's goal is to explore different ways of measuring and expressing kidney function and blood pressure in children and youth, and determining how these methods are associated with evidence of other organ damage (e.g., the heart). Dr. Zappitelli currently uses several methodologies for performing his research, mostly including observational cohort studies. The Zappitelli Lab's funding sources have included or include Canadian Institutes of Health Research, Fonds de Rrecherche du Quebec-Sante, Kidney Foundation of Canada, the Montreal Children's Hospital Research Institute, the Research Institute of the Hospital for Sick Children, and the National Institutes of Health.

Dr. Zappitelli was clinically trained in Pediatric Nephrology and obtained a Master's degree in Epidemiology & Biostatistics at McGill University. He completed a 2 year clinical and research fellowship in Pediatric Acute Care Nephrology at Baylor College of Medicine, Texas from 2005-2007. He was on staff as a Nephrologist and Clinician Scientist and as Director of the Dialysis & Apheresis program at the Montreal Children's Hospital until December 2017. In January 2018 Dr. Zappitelli transitioned to The Hospital For Sick Children/ Research Institute. He is currently a Staff Paediatric Nephrologist, Senior Scientist, and Associate Professor within the Division of Nephrology, Child Health Evaluative Science Research Program and Department of Paediatrics at the University of Toronto. Dr. Zappitelli is also an Adjunct Professor at the Faculty of Medicine of McGill University.

Novel Approaches to Improving Pharmacotherapy in Epilepsy: Machine Learning and Human Organoids

Peter L. Carlen MD, FRCPC; Krembil Research Institute; Toronto Western Hospital, University Health Network; Departments of Medicine (Neurology), Physiology, and IBBME, University of Toronto

With the tremendous advances in computer technology and cell biology, personalized pharmacotherapy is becoming a reality. This talk will outline approaches now possible for resolving the difficult quandary that clinicians often face when treating patients with epilepsy: which drug or which treatment (such as dietary therapy) is most likely to succeed in any individual patient. There are over 20 anticonvulsants available from which to choose. To go through this list attempting to find the ideal drug can take years of testing and frustration till a proper

drug or drug combination is found. Furthermore, approximately 30% of patients with epilepsy are drug resistant.

Machine Learning:
Recent advances in computer speed and storage and in machine learning paradigms, permit the mining of large databases to define an individual patient's characteristics, which can guide the clinician towards an optimized treatment plan. This plan will be focussed on that patient's specific characteristics and not on a "guideline" for the "average patient", which doesn't really exist. Colic et al. (2017) used machine learning algorithms which were trained and evaluated using features obtained from intracranial EEG (iEEG) recordings of the epileptiform discharges observed in a Mecp2-deficient mouse model of the Rett Syndrome. Previous work has linked the presence of cross-frequency coupling Index (I_{CFC}) of the delta (2–5 Hz) rhythm with the fast ripple (400–600 Hz) rhythm in epileptiform discharges. Using the I_{CFC} to label post-treatment outcomes they used machine learning classifiers for providing likelihood scores of successful treatment outcomes, which yielded predictions of successful drug treatment outcomes. Similarly in humans, one can derive a computer-based multivariate classification from a dataset of 100's of patients with epilepsy including EEG, demographics, seizure type(s), genotype, and anticonvulsant drug responses, to predict the optimal pharmacotherapy for an individual epileptic patient.

Human Cerebral Induced Pluripotential Stem Cells and Organoids:
Based on recent exciting advances in stem cell research, it is now possible to create stem cells from adult humans and induce these pluripotential stem cells (iPSCs) to form cerebral organoids, which have the detailed organization of the cerebral cortex. We have examined human cerebral organoids showing that we can measure cerebral activity both extra- and intracellularly, which is greatly increased with a convulsant. Drug resistant patients with epilepsy will be phenotyped (history including anticonvulsants taken, neurological exam, EEGs, MRI, blood tests) and genotyped in the epilepsy clinic. Fibroblasts, obtained from these patients will be treated to become iPSCs and cerebral organoids. These tissues will be kept on multi-well plates for multiple pharmacodynamic and pathophysiological testing. The patient's responses to different pharmacotherapies will be assessed and correlated with the extensive clinical and genetic profiling available clinically. This will give us an individual patient's "brain in a dish" to devise optimal treatment strategies, possibly avoiding years of fruitless clinical testing.

Peter L. Carlen
Peter L. Carlen MD, FRCPC, obtained his MD from the University of Toronto and his internship and Internal Medicine training at McGill University, completing his Neurology training at the University of Toronto. He also did postgraduate training in cellular electrophysiology for 3 years at the Neurobiology Unit of the Hebrew University of Jerusalem, Israel. He is a Professor in Medicine (Neurology), Physiology, and the Institute of Biomaterials and Biomedical Engineering at the University of Toronto. He was formerly the Head of Neurology at the Addiction Research Foundation. In 1989, he was appointed Director of the Playfair Neuroscience Unit and Neuroscience Research at the University Health Network for a 10 year term, where he is now a Senior Scientist and Head of the Division of Fundamental Neurobiology. He has over 300 peer-reviewed biomedical publications and 6 patents. His main research interests are mechanisms and control of neural synchrony and entrainment in epilepsy, mechanisms of sudden unexplained death in epilepsy (SUDEP), hypoglycemic seizures, gap junctional communication, brain state classification, and the cerebral pathophysiology of the fetal alcohol syndrome. He is also an active neurological clinician at the University Health Network (Toronto Western Hospital) with a practice focused mainly on patients with epilepsy.

Vaccinating Children Against Pain and Fear

Anna Taddio, University of Toronto

Despite their effectiveness for preventing disease, vaccinations are associated with a negative experience for many children due to the pain and fear associated with their administration. Importantly, these negative experiences can contribute to vaccine hesitancy and reduced compliance with future vaccinations, undermining vaccination. The objectives of this presentation are to describe: 1) the importance of pain and fear mitigation during vaccination in children; and 2) new evidence regarding effective strategies for mitigating pain and fear. The presentation will also include discussion about efforts underway to

incorporate pain and fear mitigation strategies into routine vaccinations in different practice settings.

Anna Taddio
Anna Taddio is a Professor of Pharmacy at the University of Toronto, and Senior Associate Scientist at SickKids. Her program of research examines: (1) the short-term and long-term effects of pain in children; (2) the effectiveness and safety of pain management interventions; and (3) evidence based practice and implementation research. Dr. Taddio currently leads a national inter-disciplinary team, Help ELiminate Pain in Kids and Adults (HELPinKids&Adults), investigating and promoting evidence-based pain management during vaccination. She has authored over 200 scientific papers and book chapters, and is the recipient of numerous awards recognizing her scholarly and advocacy achievements in pediatric pain.

CSPT Senior Investigator Award

Addiction to Cocaine: How you Take the Drug is More Important than how Much

Anne-Noël Samaha, PhD, Université de Montréal

A fundamental question in addiction research concerns how recreational patterns of drug use change the brain to promote a transition to the pathological patterns of drug use that define addiction. This is studied in animals using drug self-administration procedures. Currently, the most widely used animal model of addiction involves letting animals self-administer a drug continuously, for several hours a day. I will argue that continuous intake of large amounts of drug is actually not very good for studying the transition to addiction. I will also present data from an alternative animal model, where drug intake is intermittent, rather than continuous. This recent work is providing new ways of thinking about what is necessary and sufficient to develop symptoms of addiction.

Anne-Noël Samaha
Dr Samaha is a behavioural neuroscientist interested in the neurobiology of drug addiction, and in the long-term effects of antipsychotic treatment. She completed her PhD at the University of Michigan, with her dissertation receiving the James McKeen Cattell award from the New York Academy of Sciences. Dr Samaha completed her post-doctoral training at the Center for Addiction and Mental Health, Toronto. In 2008, she joined the faculty at the University of Montréal.

Using animal models, Dr Samaha is pursuing research on two fronts. First, she is investigating the behavioural and neural plasticity induced by chronic exposure to antipsychotic medications. Second, she is investigating the question of how the temporal dynamics of psychostimulant drug use (continuous or intermittent intake, fast or slow drug onset) determine outcome.

Dr. Samaha has been an FRQS research scholar since 2009. Her research is also funded by CIHR, the Canada Foundation for Innovation, and NSERC

Poster Session 1

CSPS and CC-CRS

Wednesday, May 23

Poster Session 1

Wednesday, May 23

Biomedical Sciences

1. Wrinkled Microparticles as new Microcarriers for Cell Culture Applications in Vaccine Production

Marziye Mirbagheri[1,2], Cynthia B. Elias[4], Stephen D. Waldman[1,2], Dae Kun Hwang[1,2]
[1]Department of Chemical Engineering, Faculty of Engineering & Architectural Science, Ryerson University, Toronto, Ontario; [2]Keenan Research Center, Li Ki Shing Knowledge Institute, St. Michael's Hospital, Toronto, Ontario; [4] Bulk Manufacturing, Sanofi Pasteur, Toronto, Ontario, Canada

Purpose: In vaccine production, cell culture is mainly performed using smooth spherical microcarriers, onto which the cells adhere and proliferate. However, this process is costly and complicated, because the microcarrier surfaces should be chemically modified to improve cell attachment, while the adherent cells can only be detached enzymatically. This study aims to investigate the feasibility and performance of wrinkled microparticles as alternative microcarriers. Recently, we have shown that the wrinkling patterns improve cell attachment, thus can eliminate the need for chemical surface modification. Here, we demonstrate that the adherent cells on the wrinkled surfaces can be removed by hydrodynamic shearing in a microfluidic channel. Therefore, the cell attachment and detachment on wrinkled microcarriers can be undertaken without additional treatments, leading to reduced cell culture costs and simplified cell recovery processes.
Method: The wrinkled surfaces with various wavelengths were fabricated. The primary bovine ligament fibroblast cells were cultured onto sterilized substrates using culture medium DMEM containing 10% FBS and antibiotics. After 72 hours, the substrates were transformed into sterilized microfluidic channels for cell detachment using hydrodynamic shearing. Cell response to a DMEM medium flow with a flowrate of 5 ml/min for 2.5 mins was studied.
Results: Fluorescent microscopic images of immunostained cells before and after cell detachment using hydrodynamic shearing illustrate that the cells detach or change their arrangements due to the flow. Our results indicate that the detachment efficiency depends on the flowrate as well as the wrinkling wavelength.
Conclusion: It has been shown previously that wrinkling patterns can improve cell attachment, even on protein-repellent poly(ethylene glycol) diacrylate surfaces. Here, we demonstrated that the adherent cells on wrinkled substrates can simply be removed using hydrodynamic shearing. Therefore, wrinkled microcarriers can be promising alternatives for cell culture in vaccine production.

2. S-Enantiomer of 19-Hydroxyeicosatetraenoic Acid Preferentially Protects Against Angiotensin II-Induced Cardiac Hypertrophy

Sherif M. Shoieb and Ayman O.S. El-Kadi.
Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, AB, Canada

Purpose: We have recently demonstrated that the racemic mixture of 19-hydroxyeicosatetraenoic acid (19-HETE) protects against angiotensin II (Ang II)-induced cardiac hypertrophy. Therefore, the purpose of this study is to investigate whether R- or S-enantiomer of 19-HETE confers cardioprotection against Ang II-induced cellular hypertrophy in RL-14 cells.
Methods: Human ventricular cardiomyocytes RL-14 cells were treated with vehicle or 10 μM Ang II in the absence and presence of 20 μM 19(R)-HETE or 19(S)-HETE for 24 h. Thereafter, the level of mid-chain HETEs was determined using liquid chromatography–mass spectrometry (LC/MS). Gene expression was measured using real-time PCR and Western blot analysis was performed to assess protein level of different enzymes.
Results: The results showed that both 19(R)-HETE

and 19(S)-HETE significantly decreased the metabolite formation rate of mid-chain HETEs namely 8-, 9-, 12- and 15-HETE compared to control group while the level of 5-HETE was selectively decreased by S-enantiomer. Moreover, both 19(R)-HETE and 19(S)-HETE significantly inhibited the catalytic activity of CYP1B1 and decreased the protein expression level of 5- and 12-lipoxxygenase (LOX) as well as cyclooxygenase-2 (COX-2). Notably, the decrease in the protein expression level of 15-LOX was only mediated by 19(S)-HETE. Moreover, both enantiomers protected against Ang-II induced cellular hypertrophy as evidenced by a significant decrease in mRNA expression of β/α-myosin heavy chain ratio, ANP, IL-6 and IL-8.

Conclusion: Our data demonstrated that S-enantiomer of 19-HETE preferentially protected against Ang II-induced cardiac hypertrophy via decreasing the level of mid-chain HETEs, inhibiting catalytic activity of CYP1B1, decreasing protein expression level of LOX and COX-2 enzymes and decreasing mRNA expression level of proinflammatory markers IL-6 and IL-8. Support: This work was supported by a grant from CIHR to A.O.S.E. S.M.S. is the recipient of Mike Wolowyk Graduate Scholarship.

3. Potential Neuroprotective Effects of Wild Blueberries: A Pilot Study

Rachel Ward[1], Erin Kelly[1], Poorva Vyas[1,2], Andre Igamberdiev[2], and John T. Weber[1]
School of Pharmacy[1] and Department of Biology[2], School of Pharmacy, Memorial University of Newfoundland, St. John's, NL.

Purpose: Parkinson's disease (PD) is a neurodegenerative disorder characterized by progressive loss of dopaminergic ne urons in the substantia nigra. Glutamate excitotoxicity and production of alpha-synuclein are two mechanisms implicated in the disease. Glutamate and alpha-synuclein also activate microglia, which release reactive oxygen species (ROS), leading to death of neurons. Blueberries are high in polyphenols which act as antioxidants. Antioxidants may exert neuroprotective effects by helping to clear ROS. The current study is a pilot experiment aimed at testing the effects of a blueberry fruit-enriched diet in wild-type mice, before testing the effects of a berry-enriched diet in mouse models of PD.

Methods: Wild-type mice (n=18) were fed mash of powdered rat meal and water for 4.5 weeks. The control group received 5 g plain mash each day. The experimental group received 5 g mash with 2% w/w wild blueberry. During the period of feeding, the mice completed rota-rod testing at 5, 10, and 15 rpm. Following completion of the feeding, all mice completed a novel object recognition test.

Results: Both groups displayed significant weight gain at the end of the study, indicating the mash was palatable long term. Although there were no significant differences between the control and experimental group data for rota-rod or novel object recognition, a trend in differences can be seen. In both tests, the experimental group outperformed the control group.

Conclusion: A blueberry-enriched mash is palatable to mice and could be used in a long-term study evaluating the neuroprotective effects of blueberries in a mouse model of PD. There is also potential for further research evaluating if blueberries provide a motor or cognitive benefit in normal health.

Acknowledgement: Rachel Ward is the recipient of a 2018 GSK/CSPS National Undergraduate Student Research Program Award.

4. Alpha-2C Adrenergic Receptor Expression in Rat Caudal Arteries

Kayla Kitselman[1], Noriko Daneshtalab[2], Reza Tabrizchi[3]
[1]Department of Biochemistry, Memorial University of Newfoundland; [2]School of Pharmacy, Memorial University of Newfoundland; [3]Department of Biomedical Sciences, Memorial University of Newfoundland

Purpose: The rat caudal artery has been shown to be thermoregulatory and innervated by the sympathetic nervous system; in response to cold environments the artery would remain dilated to increase blood flow. Alpha 2-adernergic receptors are G-protein coupled receptors that are primarily neuronal in origin. They are shown to change its location in the cell in response to changes in temperature. The aim of our study was to determine whether alpha-2C adrenergic receptor regulates vascular tone and thus be involved in thermoregulation in the rat caudal arteries.

Methods: Sprague Dawley rats (SDR) were sacrificed and their caudal arteries were collected and incubated ex vivo in Krebs buffer at 24^{o}C or

37°C for one hour. The samples were then fixed and blocked in paraffin. 6 µm sections of the samples were cut then placed on positively charge glass slides for immunofluorescence experiments to stain for alpha 2C receptors. Upon staining, confocal imaging was performed using Fluoview 1000. The images were then semi-quantified using ImageJ with FIJI plugin and the mean grey value of the area outside of the vascular smooth muscle of the images was used for semi-quantification.

Results: Qualitative analysis showed increased expression of alpha-2C adrenergic receptors in 24°C samples compared to 37°C samples. Semi-quantification and statistical analysis of the images showed a significant difference ($p<0.05$) in the alpha-2C adrenergic receptor expression between the two sample groups (n=4/group).

Conclusion: The increase in alpha-2C adrenergic receptor expression at colder temperatures supports the idea that alpha-2C adrenergic receptors maybe involved in the thermoregulatory mechanism of rat caudal arteries.

5. Upregulation of Reduced Folate Carrier (RFC) by Vitamin D Enhances Folate Uptake at the Blood-Brain Barrier (BBB)

Camille Alam[1], Constantine Georgiou[1], Richard H. Finnell[2], I. David Goldman[3], Reina Bendayan[1]
[1]Department of Pharmaceutical Sciences, Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, Ontario, Canada; [2]Departments of Molecular and Cellular Biology and Medicine, Baylor College of Medicine, Houston, Texas, USA; [3]Department of Molecular Pharmacology, Albert Einstein College of Medicine, Bronx, New York, USA

Purpose: Folates are essential for brain development and function. Folate transport is mediated by three major transport pathways, i.e., RFC, proton-coupled folate transporter (PCFT) and folate receptor alpha (FRα), known to be regulated by ligand-activated nuclear receptors. Cerebral folate delivery occurs predominantly at the choroid plexus through concerted actions of FRα and PCFT, but mutations in these transport systems can lead to early childhood neurodegeneration. Our laboratory has demonstrated *in vitro* that functional expression of RFC at the BBB and its upregulation by the vitamin D nuclear receptor (VDR) could provide an alternative route for brain folate delivery. This study aims to further investigate the role of VDR in the regulation of RFC at the BBB, using a FRα knockout mouse model.

Methods: qPCR and immunoblotting were used to assess relative expression of folate transporters in FRα knockout and wild type mice. To examine the effect of VDR activation on RFC, mice were treated intraperitoneally with the VDR ligand, calcitriol ($1,25(OH)_2D_3$; 2.5 µg/kg), or vehicle (corn oil) every other day for 8 days. On day nine, animals were sacrificed and tissues (kidney, liver, and isolated brain capillaries representative of the BBB) were collected for quantification of RFC expression.

Results: Treatment with calcitriol induced RFC mRNA expression in the brain capillaries (1.5-fold), kidney (1.3-fold), and liver (2-fold) of wild type and FRα knockout animals compared to vehicle.

Conclusion: Induction of RFC expression in brain capillaries of FRα knockout mice through VDR activation supports our previous *in vitro* findings and suggests a potential role for RFC in enhancing folate brain permeability. This work will elucidate whether folate transport by RFC can compensate for the loss of FRα function, thereby potentially constituting a novel treatment strategy for neurometabolic disorders caused by cerebral folate deficiency. *(Supported by NSERC*)

6. Examining the Cholesterol Synthetic Pathway in the Search for New Druggable Targets for Glioblastoma

Wendy Siu, Andy Yang, Lilia Magomedova, Graham Macleod, Nishani Rajakulendran, Stephane Angers and Carolyn L. Cummins.
Faculty of Pharmacy, University of Toronto, Toronto, Ontario, Canada

Background: Glioblastoma (GBM) is the most aggressive form of primary brain cancer with fewer than 5% of patients surviving beyond five years. Genome-wide CRISPR screens revealed enzymes in the cholesterol biosynthetic pathway: squalene synthase (FDFT1), squalene epoxidase (SQLE), and lanosterol synthase (LSS), are essential for survival of GBM cells but not for other oncogenic cells. We hypothesized that inhibiting/disrupting the cholesterol biosynthetic pathway may be a unique avenue for targeting GBM.

Methods: Two patient-derived primary GBM stem cell lines (GBM510 and GBM514) and one normal neural stem cell line were propagated in culture.

Cholesterol and its intermediates were extracted using MTBE and analyzed by LC/MS/MS. To validate the genome-wide results, we knocked out the enzymes using CRISPR and then performed rescue experiments with exogenous cholesterol or its intermediates measuring cell viability with Alamar Blue. Small molecule inhibitors RO48-8071 (LSS), terbinafine (SQLE), and zaragozic acid A (FDFT1) were also tested.

Results: The levels of cholesterol and intermediates were similar in all three cell lines. Cholesterol, lanosterol and desmosterol, downstream of LSS, were able to rescue LSS knockout GBM cells but squalene, the upstream precursor, had no effect. Zaragozic acid (100μM) had no effect on the growth of any of the cells. Compared to vehicle, terbinafine hydrochloride (>25μM) and RO48-8071 (10μM) inhibited the growth of both the GBM and control cell lines. Compared to vehicle, RO 48-8071 at 100nM was able to selectively inhibit the growth the GBM cell lines without impacting the control cells.

Conclusions: The cholesterol biosynthetic pathway is active in GBM cells but the level of cholesterol produced is not different between GBM and normal neural stem cells. The LSS gene identified from the CRISPR screen could selectively inhibit the growth GBM cells but not the normal neural stem cells indicating that lanosterol synthase may be a druggable target.

Acknowledgement: Wendy Siu is the recipient of a 2018 GSK/CSPS National Undergraduate Student Research Program Award.

7. Role of Peroxisome Proliferator-activated Receptor-γ (PPARγ) in Regulating Inflammatory Signalling in Acute and Chronic Rodent Models of HIV-1 Associated Brain Inflammation

Amila Omeragic[1], Nareg Kara-Yacoubian[1], Jennifer Kelschenbach[2], David J. Volsky[2] and Reina Bendayan[1]

[1]Department of Pharmaceutical Sciences, University of Toronto, Toronto, Ontario, Canada; [2]Department of Medicine – Division of Infectious Diseases, Icahn School of Medicine at Mount Sinai, New York City, USA

Purpose: Despite the use of antiretroviral therapy for the treatment of HIV-1 infection, cognitive impairments remain prevalent due to persistent viral replication and associated brain inflammation. Cellular targets in the brain include microglia and astrocytes which in response to infection release inflammatory markers and viral proteins (i.e., gp120, Tat). PPARs are ligand-activated transcription factors that play a role in glucose/lipid metabolism. Compelling evidence suggests that the PPARγ isoform exerts anti-inflammatory properties in neurological disorders. The goal of this study was to examine the role of PPARγ in the context of HIV-associated brain inflammation *in vivo*, in acute and chronic rodent models.

Methods: In the acute model, rats were administered an intracerebral ventricular (ICV) injection of the HIV-1 viral protein, $gp120_{ADA}$ and received PPARγ agonist (rosiglitazone). Inflammatory markers were measured using qPCR (24h post ICV). Activation of transcription factor (NF-kB) was quantified by immunoblotting (5h post ICV). In the chronic model, mice were administered an intracranial injection of ecotropic HIV-1 (EcoHIV) which is a chimeric strain of HIV where gp120 is replaced with leukemia virus gp80, rendering the virus capable of infecting mice. In this model, we quantified viral genes and inflammatory cytokines/chemokines 5d and 21d post infection and treated mice with rosiglitazone or pioglitazone.

Results: Rosiglitazone reversed the HIV-1 gp120 induced inflammatory response and inhibited NF-kB activation. EcoHIV infection significantly induced several inflammatory cytokines/chemokines 5d and 21d post infection. Detection of viral genes demonstrated productive infection. Treatment with rosiglitazone or pioglitazone for 5d reduced inflammatory responses.

Conclusions: To date, we have successfully implemented a robust model of HIV-1 neuropathogenesis i.e., the EcoHIV mouse model which recapitulates many clinical features of the disease. This model is a non-hazardous approach for investigating treatment strategies. Herein, we have also demonstrated that targeting PPARγ may provide a novel molecular target for preventing/treating HIV-associated brain inflammation.

8. Vascular Endothelial Growth Factor a Diagnostic Test for POEMS Syndrome

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Background and Aims: POEMS syndrome is characterized by poly-neuropathy, osteo-sclerotic myeloma, organomegaly, endocrinopathy, monoclonal plasma cell disorder, and skin changes. We aim: (1) to demonstrate the utility of quantitative measurement of serum levels of VEGF in the diagnosis of POEMS and the monitoring of therapeutic interventions; (2) to demonstrate that overproduction of pro-inflammatory cytokines is a characteristic of POEMS.
Methods: We studied 14 POEMS patients clinically presenting POEMS. We compare the serum levels of cytokines and chemokines between the POEMS patients with 80 patients with viral hepatitis C (HCV), 12 healthy controls, and 80 individuals with alcoholic liver disease (ALD). We quantified (ELISA pg/mL) the levels of VEGF, Interferon gamma (IFN-γ), Tumor Necrosis Factor alpha (TNF-α), Regulated-upon-Activation Normal-T-cell-Expressed and presumably-Secreted (RANTES), and Nuclear Factor kappa-B (NFκB).
Results: In POEMS patients, VEGF levels were 20 x elevated versus control, 16 x ALD, 14 x vs HCV. TNFα levels were 8x higher versus control, but significantlylower when compared with HCV or ALD patients. VEGF levels in POEMS patients decreased with therapeutic intervention. Interferon gamma (IFN-γ), RANTES levels were x10 vs, control, but not differed significantly from ALD and HCV. NFκB levels were not significantly different from HCV and ALD. The follow up of individual cytokine kinetics during the 4 years showed significant reduction in all parameters.
Conclusions: Extreme elevation of VEGF levels is diagnostic for POEMS syndrome, and should be followed to assess response to therapy.

9. Investigating the Role of the IKKβ Protein Kinase in Vascular Remodeling Events

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Purpose: The IKKβ protein kinase is an important regulator of the chronic inflammatory response and is increasingly shown to be central in vascular inflammation. As blood vessels respond to injuries, they undergo a process called “remodeling” which allows them to heal and maintain their function. However, in conditions involving chronic vascular inflammation, a dysregulation in vascular remodeling (VR) processes is observed, leading to clinical outcomes such as atherosclerosis and arterial aneurysm. The aim of this study was to better understand the role of IKKβ in modulating VR phenomena, specifically by generating IKKβ-deficient primary human aortic smooth muscle cells (HASMCs) to be used as an in vitro research tool to characterize differential VR gene expression.
Methods: LentiX 293T packaging cells were used to produce third generation lentiviral particles encoding the Cas9 endonuclease and different guide RNA sequences designed to target the human *IKBKB* gene at six different loci. Transduction of the primary HASMCs was followed by antibiotic selection giving rise to seven stable populations: populations #1 through #6 in which the *IKBKB* gene is targeted and a non-target control population. These cells were then exposed to the proinflammatory cytokine TNF-α for different periods of time. Isolated protein and RNA were used in Western blot and RT-qPCR analyses respectively to assess the activation of IKKβ-dependent proinflammatory cellular responses.
Results: The steady-state expression of IKKβ was dramatically reduced in populations #1 and #2. This was associated with a defect in TNF-α cellular signaling events, more specifically with a decrease in both IκBα phosphorylation and interleukin 6 induction.
Conclusion: Stable populations of IKKβ-deficient HASMCs were successfully generated using

CRISPR-Cas9 technology, giving rise to populations of cells which proved resistant to TNF-α-induced proinflammatory cellular responses. Further experiments will explore the effect of vasoactive proinflammatory inducers on these cells with respect to genes involved in VR.

Acknowledgement: Francis Lefebvre is the recipient of a 2018 GSK/CSPS National Undergraduate Student Research Program Award.

10. Quantitative and Qualitative Analysis of a Bioluminescent BRCA Deficient Model of Serous Ovarian Cancer

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Purpose: Currently there is a lack of *in vivo* xenograft models of BRCA deficient ovarian cancer. The purpose of this study is to develop a bioluminescent model of BRCA deficient serous ovarian cancer for real-time assessment of disease progression and treatment response.
Methods: Firefly luciferase was transfected in BRCA1 deficient OVCAR8 cells. Five or ten million OVCAR8^{luc} cells were injected intraperitoneally in 7 weeks old, female NOD/SCID mice. Bioluminescence imaging was performed weekly to monitor tumor development. Levels of IL-6, IL-8 and IL-10, which are associated with enhanced tumorigenesis and metastasis, were measured in serum and ascites using ELISA assay.
Results: Death or ethical endpoints were reached in all mice at 58±4 days post-inoculation. As determined by bioluminescence signaling, significant differences in tumor growth rate and tumor burden were not seen in animals inoculated with either 5 or 10 million cells. The model was characterized by ascites formation, distended abdomen and a high degree of tumor burden. Following post-mortem examination, disseminated disease was found in the liver, intestine, gall bladder and peritoneal wall. Regression analysis demonstrated significant correlations between bioluminescence signal and tumor weight or tumor volume (R^2 = 0.65 and 0.61, respectively). Immunoblots of OVCAR8 cells and collected tumors confirmed that a low protein expression of BRCA1 was maintained in the xenografts. A 3-fold increase in serum IL-6 and a 2-fold increase in ascites concentrations of CXCL2/MIP-2 (mouse analogue of human IL-8) and IL-10 were associated with tumor progression.
Conclusion: The BRCA1 deficient OVCAR8^{luc} model possesses characteristics that are associated with clinical features of ovarian cancer. The correlation of bioluminescent signal with tumor burden allows for real-time monitoring of disease progression and treatment response. The current model may provide a clinically relevant platform for the preclinical assessment of novel therapeutic options for serous ovarian cancer.

11. Injectable, Covalently *In Situ*-Gelling Block Copolymers for the Improved Loading and Prolonged Release of Hydrophilic Drugs

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Purpose: Poly(N-isopropylacrylamide) (PNIPAM)-based "smart" hydrogels [1] exhibit a volume phase transition at ~32°C, leading to improved entrapment of hydrophobic drugs but rapid burst-like convective release of hydrophilic drugs [2]. The lower pore size of PNIPAM hydrogels in their collapsed state offers an opportunity to significantly prolong the release of hydrophilic drugs if the initial convective burst release is minimized. In response, we synthesized *in situ*-gelling block copolymers based on PNIPAM and poly(N-(2-hydroxyethyl)acrylamide) (PHEA), a highly hydrophilic polymer that can self-associate into domains, the presence of which is hypothesized to improve uptake and to slow release kinetics.
Methods: Reverse addition-fragmentation chain-transfer (RAFT) polymerization was used to copolymerize PNIPAM with tert-butyl acrylate (tBA) to form P(NIPAM-co-tBA) (M_w ~16 kDa) followed by chain extension with HEA to form P(NIPAM-co-tBA)-b-PHEA. The molecular weight of the PHEA block length was systematically varied (2.5 kDa, 5 kDa, 10 kDa, and 20 kDa). The tBA groups were then hydrolyzed and converted to hydrazide groups via carbodiimide-mediated conjugation of adipic acid dihydrazide. These block copolymers were co-extruded via double barrel syringes with fluorescein-ovalbumin and aldehyde-functionalized PNIPAM to form protein-loaded hydrogels.

Results: Polymers with HEA block lengths of 5 kDa and 2.5 kDa at concentrations of 15 and 20 wt% formed gels within 5 minutes of mixing the functionalized precursors, while longer HEA block lengths did not form gels. Relative to PNIPAM-only hydrogels, PNIPAM-b-PHEA hydrogels showed significantly different release kinetics for fluorescein-ovalbumin as a function of PHEA block length.
Conclusion: Using block copolymers with amphoteric properties as building blocks for injectable hydrogels can address key challenges with the use of smart thermoresponsive hydrogels for drug delivery.
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12. Using PD-1 Knockout Mice to Test the Potential of Green Tea Extract and (-)-epigallocatechin-3-gallate (EGCG) to Cause Idiosyncratic Drug-induced Liver Injury

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Purpose: Idiosyncratic drug-induced liver injury (IDILI) can lead to liver failure or even death. The dominant immune response to drugs that can cause IDILI appears to be immune tolerance, and we have developed the first validated animal model by using a PD-1 deficient mouse model with anti-CTLA-4 to block immune checkpoints. Herbal products have become a significant cause of IDILI. Green tea extract, which is used for weight loss, has been associated with several cases of liver failure leading to liver transplantation or death. It is suggested that hepatotoxicity is most likely due to (-)-epigallocatechin-3-gallate (EGCG), the major catechin in green tea formulations. We hypothesize that the IDILI caused by green tea extract is immune-mediated and will be unmasked in PD-1 deficient mice.
Methods: Male and female C57BL/6J mice (n=3/group) were treated with green tea extract mixed thoroughly in their food at a dose of 250 mg/kg or 500 mg/kg for 5 weeks. PD-1 deficient mice received the same dose of green tea extract plus anti-CTLA-4 (300 μg) at days -3, -1, and every subsequent week after until endpoint.
Results: Neither dose resulted in an increase in serum ALT in wild type animals, but a dose of 500 mg/kg produced a delayed onset increase in ALT in the PD-$1^{-/-}$ females and a more acute increase in PD-$1^{-/-}$males. There was also an inflammatory mononuclear infiltrate in the livers of female PD-$1^{-/-}$ mice.
Conclusion: The increase in ALT and inflammatory hepatic infiltrate indicates the presence of liver injury in the PD-1 deficient mice. These results support the hypothesis that green tea extract can cause immune-mediated liver injury in humans and provides a method for mechanistic studies. Future work will delineate if EGCG is responsible for causing the liver toxicity.

13. Combining Statins with Radioimmuno-therapy as a Novel Therapeutic Strategy for Colorectal Cancer

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Purpose: Advanced colorectal cancer (CRC) remains the fourth leading cause of cancer-related deaths worldwide. Therefore, there is an urgent need for the development of more-successful therapies. Radioimmunotherapy can selectively target tumour-associated antigens and deliver prolonged low-dose ionizing radiation. It is well tolerated and has shown encouraging therapeutic activity in CRC; however, outcomes are far from optimal. Recently, HMG-CoA reductase inhibitors (statins) have been implicated as radiosensitizers, representing a potential effective combination with radioimmunotherapy.
Methods: We investigated whether simvastatin can radiosensitize CRC cells, and if it can be effectively combined with radioimmnotherapy in vivo, using a

radiolabeled anti-CEA antibody. We evaluated cell viability in response to simvastatin and irradiation in four human CRC cell lines (SW48, SW1222, LoVo, LS174T). We then evaluated the therapeutic effect of simvastatin and radioimmunotherapy in vivo in the human SW1222 CRC xenograft model. Efficacy was evaluated based on tumour growth delay and survival.
Results: Irradiation or simvastatin significantly reduced cell survival in a dose-dependent manner, and a further significant reduction in survival was observed with the combination in all cell lines. The combination of simvastatin with radioimmunotherapy significantly and synergistically reduced in vivo tumour growth and prolonged survival of mice.
Conclusion: Our results demonstrate significantly enhanced therapeutic efficacy with the combination of simvastatin and radioimmunotherapy in CRC, which could potentially translate into well-tolerated successful clinical outcomes.

14. Effect of Female Sex Hormones and Their Derivatives on Amyloid Beta Aggregation

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Purpose: Alzheimer's disease (AD) is the most prevalent form of dementia, accounting for over 60% of all cognitive dysfunction in the elderly. There are three hallmark features that have been identified in Alzheimer's patients (i) deficiency in cholinergic neurons (ii) accumulation of insoluble amyloid beta (Aβ) plaques and (iii) the formation of neurofibrillary tangles. The Aβ cascade is an attractive target in developing potential therapy options to treat AD. We investigated the effect of natural and synthetic female sex hormones in preventing the formation of neurotoxic Aβ aggregates.
Methods: The anti-Aβ activity of sex hormones was evaluated by fluorescence spectroscopy and the binding interactions were investigated by molecular docking studies.
Results: The Aβ40 aggregation kinetics assays results demonstrate that naturally occurring estrogens or their semi-synthetic derivatives exhibit anti-Aβ activity whereas progesterone and its synthetic derivatives were generally inactive.
Conclusion: These studies show that use of female sex hormones could provide beneficial effects in post-menopausal women who are at a greater risk of dementia and might provide cognitive benefits.
Acknowledgement: Stephanie De Jong is the recipient of a 2018 GSK/CSPS National Undergraduate Student Research Program Award.

Clinical Sciences & Pharmacy Practice

15. Aspirin and Other Non-Steroidal Anti-Inflammatory Drugs Interactions: A Systematic Review

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Purpose: Some clinical trials and epidemiological studies suggest reduced cardiovascular (CV) risk for non-Aspirin non-steroidal anti-Inflammatory drugs (NANSAIDs) if used along with low-dose of Aspirin which is believed to be through its anti-platelet action. In the meantime, *in vitro* and *ex vivo* studies suggest that NANSAIDs may mask the CV benefits of Aspirin. We, therefore, carried out a comprehensive systematic search to assess the CV risks of concomitant use of NANSAIDs and Aspirin.
Methods: We searched MEDLINE, EMBASE, CINAHL, Web of Science, and the Cochrane Library databases up to August 2017 using the following keywords: acetylsalicylic acid, Aspirin, NSAIDs, nonselective NSAIDs, cyclooxygenase-2, NSAID/aspirin interaction, adverse effects and platelet effects. Clinical Trials Registry platforms and bibliographies of included studies were searched for relevant additional studies. Titles and abstracts of included studies were retrieved and screened independently by two reviewers to identify potentially relevant studies. The risk estimates of CV risk (OR, RR or HR; 95% CI) were extracted and the quality of included epidemiological studies were assessed.
Results: In total, 32 eligible studies (20 biochemistry studies and 12 observational trials) on the interactions of Aspirin and NANSAIDs were found. *in vitro* studies suggest that the anti-platelet effect of Aspirin is diminished when combined with

some NANSAIDs like ibuprofen, naproxen and refecoxib. Nevertheless, with a few exceptions, studies suggest that the risk of myocardial infarction and death is comparable between patients who used Aspirin alone or with ibuprofen, naproxen, diclofenac, meloxicam, celecoxib or rofecoxib; i.e., NANSAIDs do not reduce the cardioprotective effect of Aspirin.
Conclusion: There does not seem to be an increased risk of myocardial infarction or death among patients who use long term Aspirin and NANSAIDs concomitantly compared with Aspirin alone. The possibility of a transient short-term therapeutically relevant interaction between these drugs remains to be studied.
Funding: University of Alberta Self-Directed Grant and Studentship from King Saud University.

16. Needs Assessment and Online Program for Physiotherapists in Alberta Regarding Physical Function and Drugs

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Purpose: To identify learning needs of practicing physiotherapists in Alberta regarding medications, and to translate these identified needs into learning activities.
Methods: An online survey was compiled from existing literature regarding self-identified learning needs of health professionals, and a scoping review that was previously conducted by this research team. Demographic questions regarding physiotherapists in Alberta was obtained from the 2015 Alberta Physiotherapists Association Annual Report. The survey was administered through the University of Alberta IT department with one original email and 2 reminders at two-week intervals. The survey feedback, scoping review, and Health Canada Drug and Health Products Safety Review were used to outline the content for continuing education modules. The online modules were outlined and guided by the online learning format used by the Faculty of Rehabilitation Medicine, University of Alberta. The modules were presented for peer review to Rehabilitation Medicine. The study was approved by the University of Alberta Health Research Ethics Board.
Results: The survey was distributed to 1,884 physiotherapists registered with the Alberta Physiotherapists Association with 362 responses. 41% of the responders had over 20 years of clinical experience, 52% worked in general practice. The responders practiced in either Edmonton or Calgary (57%), with the most common specialty reported being orthopaedics (14%). Physiotherapists reported being unfamiliar with statins (67%), psychiatric medications (63%), antihyperglycemic agents (55%), and medications affecting the stomach (e.g. PPIs; 67%). A four module accredited online program was subsequently outlined with topics including: (1) drug induced tendinopathy; (2) drug induced myalgias arthralgias, and rhabdomyolysis; (3) physical function and drugs in the elderly; and (4) antidepressants and post-stroke motor recovery.
Conclusion: This project demonstrated that physiotherapists identified a number of medication-related learning needs for professional practice, and learning needs can be addressed in health professional continuing education through interprofessional collaboration.
Acknowledgement: Jonathon Thomson is the recipient of a 2018 GSK/CSPS National Undergraduate Student Research Program Award.

17. Nocturnal Hypoglycemia Associated with Bedtime Insulin Mixture Administration in Hospitalized Patients

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Purpose: Administration of regular or rapid-acting insulin without concomitant carbohydrate ingestion increases hypoglycemia risk. Bedtime administration of insulin mixtures, which contain regular or rapid-acting insulin, has been observed in our hospitals. Our aim was to compare nocturnal hypoglycemia rates following insulin mixture administration at bedtime compared to suppertime in hospitalized patients.
Methods: Insulin mixture orders were extracted from the pharmacy information system of the Queen Elizabeth II Health Sciences Centre between January 1, 2016 and December 31, 2017. Retrospective chart

review was conducted on inpatient visits. Visits were excluded if length of stay was less than 48 hours, if the patient received less than two administrations of an insulin mixture, or if blood glucose readings between 2200h and 0900h were not documented. Insulin mixture administration was categorized as supper if prior to or at 1800h and bedtime if after 1800h. Nocturnal hypoglycemia was defined as point-of-care blood glucose reading of less than 4mmol/L between 2200h and 0900h. Rates were calculated as instances of nocturnal hypoglycemia, divided by total administrations per visit. Descriptive analyses and a Mann-Whitney test were performed.

Results: A total of 123 patient visits were included, mean age 73.4 (±9.9) and 56.1% male. For those in the supper administration group (n=102), the mean nocturnal hypoglycemia rate was 4.26% compared to 15.24% (p=0.143) in the bedtime administration group (n=21).

	Supper	Bedtime
Number of patient visits	102	21
Number of insulin administrations	867	142
Mean insulin administrations per visit (SD)	8.50 (±7.80)	6.76 (±5.66)
Mean nocturnal hypoglycemia rate per visit (SD)	0.0426 (±0.1096)	0.1524 (±0.2690)

Conclusion: To our knowledge, this is the first study to examine the safety of insulin mixture administration at bedtime. When compared to suppertime administration, bedtime administration of insulin mixtures was associated with a higher rate of nocturnal hypoglycemia, however, this difference was not statistically significant.

Acknowledgement: Kelsey Mann is the recipient of a 2018 GSK/CSPS National Undergraduate Student Research Program Award.

Drug Delivery and Pharmaceutical Technology

18. Cytotoxicity Profiles of Lanthanide Compounds within Human Kidney (HEK-293), Liver (HEPG2), and Osteoblast (HOb) Cells in addition to Murine Pre-osteoclast (RAW 264.7) Cells

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Purpose: Our team has developed a promising lanthanide compound (LaXT) that has the potential to treat bone density disorders such as osteoporosis. Recently published animal studies found that La^{3+} preferentially accumulates in tissues and particularly in bone. The purpose of this study is to develop a cytotoxicity profile for the lanthanum compounds in human kidney and liver cells as well as bone-related human osteoblast cells after a preliminary investigation into the IC_{50} of the compound in a prostate cancer cell line (C4-2).

Method: For all cell lines, 5000 suspended cells in 100 µL of complete culture medium, were seeded in 96-well plates and allowed to attach overnight. Subsequently, cells were treated with varying concentrations of each lanthanum compound for 48 or 72 hours then cell viability was determined using CellTiter 96® AQ_{ueous} One Solution Cell Proliferation Assay (MTS). Data were plotted in GraphPad Prism5 and analyzed using two-way ANOVA with Bonferroni post hoc tests.

Results: Preliminary investigation into the cytotoxicity of LaXT in C4-2 cells demonstrated that the concentration when 50% of cell death occurred was 355.3 µM. Limited toxicity was observed in HEK-293 human kidney cells, HepG2 human liver cells (Figure 1), and RAW264.7 murine pre-osteoclast macrophage cells treated with <300 µM of LaXT or $LaCl_3$ (docetaxel 25nM and 1% (v/v) Triton X-100 were positive controls used to achieve

an average of approximately 60% and 99% cell death respectively). In HOb bone-related human osteoblast cells, no significant reduction in cell viability occurred until concentrations of LaXT or $LaCl_3 \geq 1000$ μM).
Conclusion: The present study shows that the LaXT compound has only limited *in vitro* toxicity at very high concentrations in the human kidney and liver cells with similar toxicity profiles in bone-related human osteoblast and murine pre-osteoclast cell lines.
Acknowledgements: Funding provided by a Saskatchewan Health Research Foundation (SHRF) Establishment Grant to KMW, EKW, JC, CO and DC. Grace Cuddihy is the recipient of a 2018 GSK/CSPS National Undergraduate Student Research Program Award.

19. Preparation and Solidification of Esculetin Nanocrystal: Towards an Innovative Approach for Hyperuricemia

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Purpose: In a previous study, esculetin illustrated the possibility to treat hyperuricemia. As a poorly aqueous soluble substance, its therapeutic efficacy maybe limited. Nanocrystals are a dosage form to improve bioavailability by enhancing the saturation solubility. The study aimed to prepare esculetin nanocrystals using a small-scale wet bead milling approach. The solidification methods, morphology, saturation solubility and stability of esculetin nanocrystals were also investigated.
Method: The esculetin suspension (3.0% w/w esculetin and 3.0% w/w Povacoat™) were milled at 800 rpm for 3 days at room temperature. The particle size was measured using a Zetasizer ZS 90. The suspension was dried by spraying-dry and freeze-drying methods. The transmission electron microscopy (TEM) and scanning electron microscopy (SEM) were employed to observe the morphology of the dried powders. The saturation solubility was evaluated at pH 1.2, 4.5 and 6.8 buffers using a shake-flask method. The fresh suspension and dried powders were stored in capped glass flasks at 4°C for a stability test.
Results: The milled suspension had a particle size of 187.7±1.4 nm, with a polydispersity of 0.179±0.029. For both drying methods, there was no size change observed. The particle sizes were uniform and no agglomeration was observed under TEM. The spray-drying process caused spherical agglomerates visible by SEM. The saturation solubility of esculetin increased 1.2-1.5 folds in nanocrystals compared with the raw material. The nanosuspension and dried nanocrystals were stable during 90 days at 4°C.
Conclusion: This study revealed that an esculetin-Povacoat™ nanocrystal was successfully produced using a small-scale approach. Nanocrystals have the potential to enhance the bioavailability of esculetin.

20. Core-Shell Spray Dried Dry Powder Vaccines for Controlled Enteric Delivery

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Purpose: Current global vaccination programs are challenged by costs associated with vaccine cold chain storage and administration. A solid oral dosage form for vaccines would alleviate these costs but is difficult to produce due to general vaccine instability and the complication of bypassing the gastric barrier. We have developed a novel consecutive spray drying method for this purpose, demonstrated with dry powder encapsulated recombinant replication deficient human type-5 adenovirus (AdHu5) and vesicular stomatitis virus (VSV) by employing an anionic copolymer as the enteric coating.
Methods: A two step spray-drying procedure was developed using a BÜCHI B290 spray dryer. Step 1 featured the viral vector encapsulated with a stabilizing sugar matrix for purposes of thermal stability. Step 2 involves the microparticles to be suspended in ethanol with Eudragit® L100 polymer (Evonik Industries) and spray dried again. Particle properties and coating efficiency were assessed with and without the active biological ingredient. *In vitro* viral activity was determined by GFP assay.
Results: Up to 25% of the starting material was fully encapsulated within the enteric coating and encapsulation efficiency was largely dependent on spray gas flow rate and solids concentration in the feed. Coated particles retained *in vitro* AdHu5 and VSV activity after testing in gastric-like acidic

conditions while uncoated controls resulted in complete activity loss.
Conclusion: The overall encapsulation efficiency was low (25%) but could be improved by adjusting the spray drying process parameters. Most importantly, retained viral activity was demonstrated for these coated vaccine powders after incubation in acidic conditions that simulated the gastric barrier.

21. Repetitive On-demand Drug Delivery by External Triggering of Injectable Magnetic Hydrogels Incorporated with Glass Transition (T_g) Switchable Nanoparticles

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Purpose: Chronic local pain management, treatment of infections, insulin delivery, and chemotherapy would benefit from repeated, pulsatile, localized, and remotely-triggered drug delivery. By co-encapsulating superparamagnetic iron oxide nanoparticles (SPIONs) that can induce localized heating upon application of an alternating magnetic field (AMF) together with glass transition temperature (T_g) switchable nanoparticles inside an injectable *in situ* gelling hydrogel, a minimally-invasive strategy to achieve repetitive localized on-demand drug release is demonstrated.
Method: We synthesized hydrophilic SPIONs by co-precipitating iron (III) and iron (II) chloride followed by coating with polyethylene glycol. Drug-loaded T_g switchable nanoparticles (T_g ~39°C) were synthesized through the miniemulsion polymerization of butyl and methyl methacrylate. Injectable *in situ* gelling hydrogels were prepared by mixing hydrazide-functionalized carboxymethyl cellulose with aldehyde-functionalized dextran using a double-barrel syringe equipped with a mixer. Both temperature- and pulsed AMF-based drug release of rhodamine B-loaded nanocomposite hydrogels was tracked via fluorescence.
Results: Temperature-based drug release experiments indicated a 4-fold increase in rhodamine release between the on-state (45°C) and off-state (37°C). Pulsed AMF-based release studies showed 2-fold enhancement of rhodamine B release between on-state (pulsed AMF) and off-state (no AMF). A similar triggered release profile was attained when a pulsed AMF was applied after one week. All the nanocomposite hydrogel system components showed promising cytocompatibility.
Conclusion: Remote magnetic triggering of the developed T_g switchable nanocomposite injectable hydrogel by the application of a pulsed AMF can provide a minimally-invasive approach for localized repetitive on-demand drug delivery over prolonged periods of time, with good resolution between the on- and off-states.

22. Dynamic PEGylation Reduces the Viscosity of Concentrated Protein Solutions

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Purpose: Proteins in solution tend to self-assemble and oligomerize at high concentration, resulting in important increases in viscosity beyond what is acceptable for injection. This project investigates the means to reduce the viscosity of concentrated protein solutions using a newly discovered class of additives to address manufacturing and formulation challenges posed by high viscosity.
Methods: We recently developed new chemistry, using phenylglyoxals (PGO), to reversibly graft methoxy poly(ethylene glycol) (mPEG) to the arginine residues of various proteins.[1] We have evaluated the viscosity-reducing effect of PGO–mPEG on a very high concentration solution of immunoglobulin G (IgG) as well as human serum albumin (HSA). To perform viscosity measurements, the concentrated yet isotonic solutions of the proteins (up to ~500 $mg.mL^{-1}$) were formulated with a highly-sub-stoichiometric amount of the additive.
Results: Our data showed that extremely small amounts of PGO–mPEG (~5 μM), were able to reduce the viscosity of a very high concentration (~460 $mg.mL^{-1}$) solution of IgG by ~35%. Similar results were obtained for HSA, where low concentration of the additive (500 μM) reduced the

viscosity of a highly concentrated HSA solution (500 $mg \cdot mL^{-1}$) by ~20%. Interestingly, addition of mPEG alone had no viscosity reducing effect on the IgG solution, whereas the reducing effect was seen in HSA solution in the presence of mPEG.

Conclusion: Considering how little of PGO–mPEG additive was required to impart such a large effect on viscosity of protein solutions, these results are promising. The discrepancy seen in the effect of mPEG on viscosity of IgG and HSA solutions, may be attributed to unique interaction of mPEG with each protein due to their structural differences and is currently under investigation.

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23. The Enhancement of the Poor Oral Bioavailability of Cefotaxime Sodium using Nano-mixed Micelles Formulation

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Purpose: The main purpose for this study was to investigate the ability of mixed micelles formulation (MMs) made of phosphatidylcholine (PPC) and BS (sodium deoxycholate) loaded with Cefotaxime sodium (CEF) and 3α,7α-dihydroxy-12-keto-5β-cholanate (MKC) complex to enhance the oral bioavailability of CEF in rats.

Methods: thin-film hydration method was used to prepare CEF loaded MMs using different BS concentrations. MMs were characterized, and the oral bioavailability of CEF in MMs formulation was assessed, and the pharmacokinetic (PK) of CEF-loaded MMs in comparison with CEF-BS complex and CEF aqueous solution were evaluated using 24 male Wistar rats. Blood samples were collected for up to 24 h, and CEF analyzed using a validated HPLC assay.

Results: PK data showed that the oral bioavailability of CEF in MMs was found to be (4.91 %) higher compared to the CEF in aqueous solution (1.30%). C_{max} of CEF in MMs formulation was higher (1.08 ± 0.1 μg/ml) compared to CEF-MKC complex (0.69 ± 0.1 μg/ml) and CEF in aqueous solution (0.52 ± 0.1 μg/ml). Similarly, the mean values for $AUC_{0-\infty}$ of CEF in MMs formulation was higher (3.89 ± 0.9 h.μg/ml) compared to CEF-MKC complex (1.52 ± 0.2 h.μg/ml) and CEF in aqueous solution (1.03 ± 0.4 h.μg/ml, respectively).

Conclusions: The mixed micelles formulation composed of PPC and BS was able to increase the intestinal epithelial cell efflux of drug and eventually enhance the oral bioavailability of cefotaxime sodium up to 4-fold.

24. A Mucoadhesive Lipidic Delivery System of the Adjuvant Innate Defense Regulator (IDR)-1002

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Purpose: To design a mucoadhesive nasal formulation of the vaccine adjuvant innate defense regulator (IDR)-1002 peptide, previously used systemically as a triple complex with poly(I:C) and polyphosphazene (TriAdj).

Methods: The binding properties of the TriAdj mixture were characterised by gel electrophoresis and fluorescence quenching using rhodamine-poly(I:C). Cationic liposomes comprised of didodecyl dimethylammonium bromide (DDAB), dioleoyl phosphatidylethanolamine (DOPE) (60:40 mol:mol) and DDAB, L-α-phosphatidylcholine (egg PC) and DOPE (45:45:10 mol:mol:mol) were prepared by the thin-film extrusion method. The liposomes and TriAdj were combined by simple mixing. The formed complex was characterized by dynamic light scattering, zeta potential, mucin binding and cytotoxicity in RAW267.4 macrophage cells by MTS assay. Mice were administered the complex intranasally with ovalbumin as antigen, and the immunogenic response was measured by ELISA (plasma IgG1, IgG2) and Elispot assays (spleen IL-

5, INF-γ).
Results: IDR-1002 peptide, polyphosphazene and poly(I:C) self-assembles in solution forming an anionic complex, demonstrated by altered electrophoretic mobility in agarose gel, co-elution on size exclusion chromatography and fluorescence quenching of rhodamine-labeled poly(I:C). TriAdj+ cationic liposomes were prepared at several molar ratios to determine optimal size stability and desired positive charge. Stable particles (<200nm over 24h) showed mucin binding of DDAB/DOPE+TriAdj was greater than DDAB/EPC/DOPE (45/45/10)+TriAdj. Exposure of RAW267.4 cells to TriAdj alone vs. lipid-complexed TriAdj indicated that DDAB/DOPE (60:40) and DDAB/EPC/Chol (45:45:10) complexation reduced TriAdj toxicity. Mice administered either TriAdj alone or the lipid-complex TriAdj indicated a significantly greater immune response with lipid complex-TriAdj (Fig 1), with IgG1>IgG2, a dose-response with the IDR-002 peptide content (2μg vs 10μg/dose), and a differential IgG1 vs IgG2 response based on the lipid composition.
Conclusion: A mucoadhesive cationic lipid-based formulation of the TriAdj IDR-002 peptide adjuvant is a potential approach for nasal administration of a vaccine product.
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25. *In vivo* Wound Healing Effect of G-CSF Loaded Nanofiber/Nanoparticle Composite

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Purpose: Wound healing could be promoted by an extracellular matrix (ECM) that release the growth factors in the controlled manner. In skin regeneration process human granulocyte colony stimulating factor (G-CSF) is considered as the prominent growth factor. Herein we aimed to prepare chitosan nanoparticles (NPs) as the framework for controlling the release of G-CSF and then incorporated the acquired NPs into the Poly (ε-caprolactone) (PCL) nanofibers for wound dressing.
Method: The G-CSF-loaded chitosan NPs prepared and then incorporated into the PCL nanofibers using suspension electrospinning method. The nanofibers then surface coating with type I collagen. The characteristics and *In vivo* efficacy of the fabricated scaffold evaluated.
Results: G-CSF-loaded chitosan NPs with average diameter of 180nm prepared. The nanofibers of 400nm acquired by incorporating the NPs into the PCL. The scaffold of nanofibers preserved the G-CSF structure against the harsh condition of electrospining process. It is considered nontoxic. The prepared scaffold not only could accelerated the wound healing by providing sustained release of G-CSF, it could also prevented further contamination of the wound.
Conclusion: The designed scaffold showed suitable proliferation of stem cells with well-adherent morphology. The histopathological results revealed the significant acceleration in skin regeneration comparing to the control groups. The designed scaffold also showed some beneficial properties; i.e. superior fibroblast maturation, collagen deposition enhancement, and minimizing the inflammatory cells. In general, the designed G-CSF loaded nanofibrous system could develop a suitable supportive dressing for wound healing.
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26. Segmented Intravaginal Ring for Dual Delivery of siRNA-encapsulated Nanoparticles and Hydroxychloroquine as a Prevention Strategy for HIV Infection

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Purpose: Microbicides are an excellent alternative to condoms to help reduce transmission of human immunodeficiency virus (HIV). An intravaginal ring (IVR) would be a suitable platform that can provide controlled delivery of drugs within the female genital tract. We propose to develop a segmented combination IVR whereby one-half of the IVR will be loaded with hydroxychloroquine (HCQ), an immuno-modulatory drug that can induce a quiescent state in T-cells and the other half will be coated with a pH-responsive film for the rapid release of small interfering RNA (siRNA)-encapsulated nanoparticles (siRNA-NP) targeting

CCR5 gene, triggered by an increase in vaginal pH due to the presence of seminal fluid as a strategy for preventing HIV infection.
Methods: Solid lipid nanoparticle made of glyceryl monosterate and L-α-phosphatidylcholine was used to encapsulate siRNA using double emulsion method, mixed with pH-sensitive polymer (Eudragit L100) and used to coat a matrix-type IVR segment, fabricated by injection molding from polyurethane. HCQ was loaded in a reservoir-type IVR segment. A release study was performed for each segment. The biocompatibility of the IVR was evaluated on cervicovaginal epithelial cell lines and on vaginal flora *Lactobacilli*.
Results: IVR segments coated with a pH-sensitive polymer rapidly released fluorescent NP at pH8.2 (12.8±1.7%) at 4 hours' time point but negligible amount at pH4.2 (0.26±0.042%). The reservoir-type IVR segment containing HCQ continuously released drug up to 21 days with a near zero-order release profile (R^2 value =0.99) with a mean daily release of 17.01±3.6μg/mL. The IVR segments were not toxic to the vaginal cells or microflora. The relative gene expression of CCR5 in cells treated with the siRNA-NP was significantly reduced with 58.60±17.36 % of gene reduction.
Conclusion: We describe an IVR system capable of controlled release of HCQ and also siRNA-NP at high pH and non-cytotoxic towards lactobacilli and vaginal/cervical epithelial cells.

27. Pharmacokinetics and Biodistribution of Traceable Poly(ethylene oxide)-*block*-poly(ester) Based Micellar Formulations of Diclofenac: The Effect of Poly(ester) Structure

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Purpose: Nonsteroidal anti-inflammatory drugs are associated with elevated cardiovascular (CV) risk, depending on the extent of their accumulation in the heart and kidneys. We have developed poly(ethylene oxide)-*block*-poly(ε-caprolactone) (PEO-b-PCL) micelles encapsulating diclofenac ethyl ester (DFEE) which favourably altered the pharmacokinetics and disposition of diclofenac in rats. Herein, we investigated whether modifying the PCL structure to poly(α-benzyl-carboxylate-ε-caprolactone) (PBCL) in micelles can induce further changes to the disposition of delivered diclofenac.
Methods: DFEE was encapsulated in traceable (Cyanine-5.5 attached) PEO-PBCL (PBCL-TM) or PEO-PCL micelles (PCL-TM). The micelles were characterized for their size distribution, DFEE encapsulation, and *in vitro* release. Diclofenac pharmacokinetics and tissue distribution was studied at 24 h following intravenous administration of micellar formulations or free diclofenac (n=3). Excised organs *were* fluorescent imaged.
Results: An average diameter of 37.2±0.06 nm was observed for PBCL-TM which was significantly smaller than that for PCL-TM (45.1±0.06 nm). The diclofenac concentration was comparable for both PBCL-TM and PCL-TM in blood and kidneys, significantly higher than free diclofenac in blood (2.3±1.4 and 1.9±0.6 μg/mL for micelles, respectively, vs below detection), and significantly lower than free drug in the kidneys (0.4±0.3, 0.5±0.5, vs 1.5±0.3 μg/g). In heart, PBCL-TM showed significantly lower diclofenac levels compared to PCL-TM and free diclofenac (0.3±0.03 vs. 0.5±0.1, 0.8±0.1 μg/g). In liver and spleen, treatments showed comparable diclofenac concentrations. Both micellar formulations similarly reduced diclofenac partition in the heart and kidneys (heart:blood ratios of 0.4±0.1, 0.7±0.2, and 4.4±0.7 and kidney:blood ratios of 0.8±0.06, 1.2±0.4, and 5.5±2.1 for PBCL-TM, PCL-TM, and free diclofenac, respectively). Near-infrared fluorescence images showed micellar carrier tissue accumulations in-line with those achieved for diclofenac.
Conclusions: PBCL based micelles further improved the biodistribution of diclofenac compared to PCL based micelles evidenced by reduced drug accumulation in the cardiac tissue. Both micelles show strong potential for a cardiac-safe delivery of diclofenac.

28. Development of Mycophenolate Mofetil (MMF) Immunosuppressant as Sustained Release Oral Nanoparticles

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Purpose: To reduce dosing frequency and improve drug adherence, mycophenolate mofetil was formulated as sustained-release mucoadhesive oral polymeric nanoparticles (CS-PNPs).
Methods: MMF nanoparticles (CS-PNPs) were prepared by a modified single-emulsion solvent evaporation method with low, medium and high molecular weights of acid-capped polylactic-co-glycolic acid (PLGA) or polylactic acid (PLA), coated with chitosan. Surfactant type, surfactant concentration and polymer concentration were varied in a limited matrix study to optimize particle size, encapsulation efficiency and *in vitro* drug release in simulated gastric fluid (2h) followed by simulated intestinal fluid (22h). Encapsulation efficiency and release of MMF were measured by HPLC. Differential scanning calorimetry (DSC), scanning electron microscopy (SEM) and mucin binding by zeta potential were also conducted.
Results: Nanoparticles of PLA (MW 18K-24K) and polyvinyl alcohol 0.5% as the surfactant, achieved encapsulation efficiency of 71-97% at drug-polymer ratios (w/w) of 1:3 to 1:7. Particle size varied by composition. Two optimal formulations [PLA 18-24K MW, medium MW chitosan, drug: polymer ratio 1:7 (w/w) and PLGA 24-38K MW, high MW chitosan, drug: polymer ratio 1:7 (w/w)] had high encapsulation efficiency (94.34% and 75.44% respectively) and sustained drug release with a minimal burst phase (Fig 1). DSC experiments reveal crystalline to amorphous transformation of MMF in the optimal formulation. Surface morphology of CS-PNPs shows spherical nanoparticles with minimal porosity. Mucin binding was demonstrated by change in zeta potential.
Conclusion: Two CS-PNP formulations of MMF containing PLA: medium molecular weight chitosan (1:7 w/w) and high MW PLGA: high MW chitosan (1:7 w/w) prepared by a solvent evaporation method is a potential approach towards achieving once, rather than twice daily oral sustained delivery of MMF.

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29. Fluorescence De-quenching and Albumin-induced Fluorescence Enhancement Assays to Measure Liposomal Drug Release of Camptothecins and Protein Kinase Inhibitors

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Introduction: The development of liposomal formulations with improved stability rely on empirical data collected in animals. In vitro assays have been used to predict release rates and stability of various liposomal formulations, but these often are not accurate; sometimes under-predicting how fast liposomal drugs are released in vivo. In this report, two in vitro fluorescence-based methods are presented; assays that produce reliable drug release curves and accelerate the design of optimized liposomal formulations of suitable fluorescent drug candidates. The methods are illustrated using camptothecins and a protein kinase inhibitor.
Methods: Drug release from liposomal camptothecins was measured with a fluorescence de-quenching assay. Camptothecin derivatives (topotecan and irinotecan) are quenched when encapsulated at high concentrations (>10mM) inside liposomes but fluoresce when released and are at low concentrations (<10 □M). The method to study drug release from the liposomal protein kinase inhibitor OTS964 relied on albumin-induced fluorescence enhancement. OTS964 fluorescence is low inside the liposomes and the liposomes are not permeable to albumin added to the outside of liposomes. Once OTS964 is released from liposomes it binds to albumin and fluorescence augments. Changes in fluorescence were measured by the fluorescence microscope IN Cell Analyzer 2200.
Results: Drug release of liposomal topotecan by the fluorescence de-quenching assay was approximately 60% at 4h and 80% at 8h; the same that was

observed in vivo. In addition, stability studies with this method demonstrated higher release rates with higher serum protein concentration and temperature. Drug release of liposomal OTS964 by the albumin-induced fluorescence enhancement assay was 84% at 4h after treatment with 5mg/mL octyl-glucopyranoside and 25% at 4h after administration of 0.4mg/mL saponin. The formulation was very stable with less than 10% release after 4 days in buffer only supplemented with albumin.
Conclusion: The present assays will help developing formulations in a more efficient way and without raising ethical concerns associated to animal experiments. These methodologies also allow the quantification of drug inside and outside liposomes and may be adapted to provide the necessary information to regulatory bodies in the process of liposomal drug development.

30. Pilot Scale-up and Evaluation of Starch-based Spray Dried Microcapsules as Controlled Drug Delivery and Taste Masking Device

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Purpose: To formulate, manufacture and evaluate starch-based spray dried microcapsules at both lab and pilot scale. The encapsulation of Acetaminophen and Caffeine was developed to aid in the controlled release, enhance chemical stability and mask the bitter taste.
Method: Starch 7.5% (w/w) was first dispersed in a phosphate buffer pH 6.8 using a low shear mixer. A second solution was prepared by dissolving Xanthan gum 1% (w/w) or a mixture of Kollidon VA64 and Cekol 150 into deionised water. Solutions were vigorously stirred using a low shear mixer. Acetaminophen and Caffeine were added to each solution with different drug loading (20 and 30% w/w). Finally, the two solutions were mixed and ready for spray drying. Solutions were spray dried using a lab scale spray dryer, 1.25 L batch size. The process was then scaled-up at the pilot scale with 22.5 L batch size. The resulting microcapsules at both scales were collected and characterised using SEM and the In-Vitro release kinetic was then evaluated.
Results: Spray drying process at the lab scale was successfully perfumed and critical process parameters optimized**.** The process was also successfully scaled-up at the pilot scale. Scanning Electron Microscopy imaging of the spray dried powder showed spherical microcapsules with size ranging from 1 to 10 µm. The sphericity of microcapsules was better with increasing Xanthan gum concentration. In-Vitro release kinetic at pH=6.8 showed a slower release rate compared to physical mixture of polymers.
Conclusion: Starch based microcapsules were formulated and successfully manufactured using spray drying at both lab and pilot scale. These microcapsules represent a promising device for the controlled drug delivery of drugs as well as for taste masking.

31. Determination of the Effect of Patient Posture and Fasting State on Digital Pulse Wave Features using a Novel Computational Technique, Non Invasive Vascular Risk Prediction System (NIVAR), and Potential Application for Assessment of Raynaud Phenomenon

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Purpose: A clinical trial was conducted to evaluate the effect of supine/upright and fed/fasted patient status on an index reflecting the state of the microcirculation at the tip of the finger, in the context of validating a novel computational analysis of the pulse oximetry waveform. A separate experiment was conducted to determine the influence of cold challenge to the hands on pulse waveform analysis by NIVAR in normal vs Raynaud Phenomenon patients.
Methods: Non Invasive Vascular Risk Prediction System (NIVAR) consists of an optical probe connected to a personal computer through a small-size, custom-made front-end biosignal amplifier.

Healthy subjects (9 male, 18 female, age 23-56) were recruited for a clinical trial approved by BCIT's Research Ethics Board. Groups: overnight fasting/supine, overnight fasting/seated, 1 h after food/ supine, 1 h after food/seated. NIVAR measurement was carried out twice/session for 3 monthly sessions. Statistical significance was determined by ANOVA ($p<0.10$, R statistical software, Bell Labs).
A demonstration cold challenge was performed on two volunteers, including one with Raynaud Phenomenon, with NIVAR measurements before and after cold exposure.
Results: The measured index was affected both by fasting state and by posture. The most significant difference was the combination of fasting state and posture changes: "Seated-Before Breakfast" and "Supine -After Breakfast" (males $p< 1\times10^{-5}$, females $p< 0.3\times10^{-5}$). NIVAR showed a greater change in the volunteer with Raynaud Phenomenon compared to the normal volunteer following cold challenge.
Conclusions: NIVAR has potential to evaluate digital blood flow in the clinical setting, which may be applicable to diagnosis and efficacy testing of topical treatments for Raynaud Phenomenon, a vasospastic condition of the extremities. Posture and feeding state are important factors to control in such assessments.
Acknowledgments: This work was supported by a grant from the VP Research Seed Fund, British Columbia Institute of Technology, Burnaby, BC, Canada.

32. Microemulsions: A Cure for All Ills?

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Purpose: There is a growing need for multi-drug therapies given the burden of concurrent disease in Canada.[1] Current multi-drug delivery options are limited and inefficient. Microemulsions (MEs), with their nano-size droplets, thermodynamic stability and spontaneous formation, are an effective multi-drug delivery tool; however, their formation behaviour especially with respect to emulsifying agents is not well understood.[2] This work explores the capability of various emulsifying agents to solubilize multiple active pharmaceutical ingredients (APIs). Our proof-of-concept system is a pre-natal supplement containing eleven (11) APIs of varying hydro- and lipophilicity.
Methods: Ternary Phase Diagram (TPD) mapping analysis was conducted at room temperature and 37°C for a list of five finalized surfactants in Miglyol 812 to evaluate type IV ME formation potential. Tensiometry studies using a Lauda T3 Du Nouy Ring Tensiometer established critical micelle concentration and surfactant synergism. Promising surfactant candidates were mixed with Miglyol 812 and water to form microemulsions into which all eleven (11) APIs (five lipophilic and six hydrophilic), were incorporated. Droplet size and zeta potential measurements were then performed with a Malvern Zetasizer Nano ZS.
Results: TPD mapping identified a unique surfactant combination of 1:3 Cremophor RH 40: Polysorbate 80 as most promising for ME type IV formation, with clear synergism demonstrated via tensiometry. Droplet sizes were approximately 50 nm after incorporation of all five lipophilic APIs and 88 nm after additional incorporation of the remaining six hydrophilic APIs. Zeta potential values were -15 mV and samples demonstrated 70-80% stability after rigorous centrifugation stress testing.
Conclusion: To our knowledge, this is the first time that microemulsion systems have been used in this capacity to simultaneously solubilize eleven (11) APIs of varying hydrophilicity. This work serves as a pioneer in the development of a single dose multi-API, microemulsion delivery system for complex, chronic multi-drug therapies.
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33. Development of Novel Polymeric Micellar DACHPt for Enhanced Platinum Based Chemotherapy in Colorectal Cancer

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Purpose: The parent compound of oxaliplatin,

dichloro(1,2-diaminocyclohexane)platinum(II) (DACHPt) is a potent chemotherapeutic agent with wide spectrum of anticancer activity, and no cross-resistance with cisplatin Incorporation of DACHPt in polymeric micelles may lead to changes in physiochemical properties as well as the pharmacokinetics profile of the drug, leading to a reduction in its unfavorable side effects; improved tumor accessibility and *in vivo* activity.

Method: Poly(ethylene oxide)-b-poly-(α-carboxylate-€-caprolactone) (PEO-b-PCCL) diblock copolymer was synthesized. Then, DACHPt was reacted with the polymer to form polymer-metal complex. The complex was dialyzed in water to prepare DACHPt loaded micelles. The average size of the micelles, complexed levels of DACHPt and platinum *in vitro* release from micelles was measured. ICP-MS was used to measure encapsulated and released Pt levels. MTTs assay was used to measure the cytotoxicity of DACHpt and DACHpt micelles against human colorectal cancer cell lines, HCT-116, SW-620 and HT29 for 24, 48 and 72 hours. The results were correlated to intracellular Pt levels.

Results: High drug loading was achieved reaching 50 % w/w (n=3) with a mean diameter size of 56 nm for DACHPt complexed micelles. The release profile of DACHPt from its micellar complex was sustained (only 53.6% of DACHPt was released by 120 h) compared to the free drug (96.5 % release at 7.5 h). The IC50s for both DACHPt-micelles and the free DACHPt decreased as the incubation time increased. However, the IC_{50} ranges were higher in DACHPt-micelles than the free DACHPt in all the three cell lines for all the incubation times. The cytotoxic drug levels were shown to be correlated with intracellular Pt levels.

Conclusion: Prepared micellar formulation of DACHPt has a high potential for targeted Pt delivery. **Acknowledgement**: AA was funded by Umm Al-Qura University, Mecca, Saudi Arabia. This research was supported by grants from NSERC.

34. Protein-triggered Sustained Release of FITC-dextran from Microspheres Modified with Aptamer-containing DNA Oligomers

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Purpose: Improving upon sustained drug release profiles for drug delivery to the posterior chamber of the eye can reduce the frequency of intravitreal injections necessary to treat diseases like wet-age related macular degeneration (AMD). We are developing smart, bio-responsive injectable microspheres and hypothesize that these polyelectrolyte-layered microspheres with shells of hyaluronic acid (HA) or alginate, modified with complementary DNA oligomers containing aptamer sequences, will release encapsulated FITC-dextran in the presence of specific proteins.

Methods: Hyaluronic acid (HA) and alginate are modified with DNA oligomers containing aptamer sequences specific to lysozyme, used as the protein of interest for this proof-of-concept work. HA is first functionalized with maleimide using 2-aminoethylmaleimide trifluoroacetate salt (AEM) and then modified with thiol-terminated oligomers by a Michael-type addition reaction. Alginate is modified by reacting its carboxyl groups with amine-terminated oligomers by a carbodiimide reaction. Electrosprayed calcium alginate microspheres (diameter < 250μm) are then coated with poly-L-lysine and DNA-modified HA or alginate. Swelling studies of the HA or alginate hydrogels are indicative of their modification. FITC-dextran is loaded during synthesis then released into PBS.

Results: HA was reacted to have 10-13% modification of the carboxyl groups with AEM. Lyophilized HA-AEM was then reacted with PEG-dithiol to produce control gels. Swelling studies in water showed that the water content was high at 96% ± 0.4%. Studies with calcium alginate polyelectrolyte-layered microspheres modified with aptamer-containing DNA oligomers have resulted in a burst release of FITC-dextran when incubated in lysozyme (in comparison to no changes with controls).

Conclusion: HA-AEM was successfully modified with PEG-dithiol in a Michael-type addition reaction and will be further adjusted to develop DNA-modified microspheres for sustained delivery applications. Protein-triggered drug release was observed from calcium alginate microspheres modified with DNA oligomers containing aptamers in the presence of lysozyme.

35. Effect of Synthesis Conditions on the Properties of Bone-Targeting Bisphosphonate- Conjugated Superparamagnetic Iron Oxide Nanoparticles (BP-SPIONs)

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Purpose: Superparamagnetic iron oxide nanoparticles (SPIONs) are used in a variety of biomedical applications including diagnostic and medical imaging. Over the years, attempts were been made to improve the selectivity of SPIONs by conjugating targeting ligands onto their surfaces. In a similar attempt, we conjugated SPIONs with bone seeking bisphosphonate drugs (BPs) e.g., alendronate, to target them to sites of bone mineral turnover. However, due to the presence of large and highly polar BP molecule, the chemical and colloidal stability of the formulation required attention. The aim of this study was to investigate the effect of synthesis conditions and to test different choices of organic acids to be used as linker to conjugate bone-seeking bisphosphonate (i.e., alendronate) with SPIONs.
Method: SPIONs were made using a published method and their surfaces were modified using different organic acids (e.g., citric acid, sodium citrate, poly-lactic-glycolic-acid and oleic acid). N-hydroxysuccinimide (NHS) in combination with 1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC) was employed to make the amino groups in alendronate molecules react with the carboxylic groups in the acids molecules, coated onto SPION surfaces. The resulting BP-SPIONs were characterized by Fourier transform infrared spectroscopy, dynamic light scattering, transmission electron microscopy and magnetic resonance imaging (MRI). The effect of various reaction temperatures, molar ratios, pH values and dispersion medium were studied for optimization purposes.
Results: We observed that choice of organic acid can significantly impact the nanoparticle's core size (describe); the hydrodynamic size and the amount of acid adsorption by SPION surfaces is described by the coating temperature and the length of the aliphatic chain in these acids. Overall, the coating of SPIONs improved their stability.
Conclusion: The effect of different coating materials and synthesis conditions was investigated on the physiochemical properties, colloidal stability and magnetic behavior of 30 nm bisphosphonate-conjugated superparamagnetic iron oxide nanoparticles.

36. Striking a Balance: Interactions of Pluronics and Gemini Surfactants for Gene Therapy Nanoparticles

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Purpose: Recently, the non-ionic polyoxyethylene-polyoxypropylene-polyoxyethylene triblock copolymer, Pluronic® F87 (BASF Corp.) was combined with cationic N,N'-bis(dimethylhexadecyl)-1,3-propanediammonium dibromide gemini surfactant (16-3-16) to form self-assembled nanoparticles for gene therapy. Human ovarian adenocarcinoma (OVCAR-3) cells were successfully transfected in vitro (albeit poorly) with less cellular toxicity than the commercial control, Lipofectamine® 2000. The transfection efficiency of this system might be improved by appropriate changes to the formulation (e.g. polymer composition, or relative amounts of nanoparticle components). The aim of this study was to investigate the effect of Pluronic molecular weight and hydrophobicity on the interaction between the Pluronic and gemini surfactant-plasmid DNA condensate (GS/pDNA) of the nanoparticles, and to determine the impact these interactions have on transfection efficiency.
Method: Pluronics differing from F87 by molecular weight or hydrophilic/hydrophobic composition were combined with the GS/pDNA condensate. Critical aggregation concentrations of Pluronic/GS/pDNA mixtures (with varying Pluronic mole fraction), were determined by tensiometry, and used to estimate the mixing behaviour of each system (e.g. synergism vs. antagonism, and the strength of interaction). Dynamic light scattering and laser Doppler electrophoresis, provided size and charge measurements, respectively, of the complete nanoparticles. In vitro transfection efficiency and cell viability was quantified using flow cytometry.
Results: The previously tested F87/GS/pDNA systems have strong synergistic interactions (interaction parameter, β = -18 to -27). The strength of this attraction can be increased by decreasing the molecular weight or decreasing the hydrophobicity

of the Pluronic component of these nanoparticles. In vitro transfection efficiencies decreased with stronger synergistic interactions; however, a reduction in the system's synergism or even slight antagonism (by replacing F87 with L121) did not increase transfection.
Conclusion: These results suggest synergism is required for successful transfection with Pluronic/16-3-16/pDNA systems. However, too much synergism within the formulation may prevent nanoparticle dissociation required for successful gene transcription.

37. Modulating Physiochemical Properties of a Small Peptide Drug by Chemical Conjugation

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Purpose: According to the National Institutes of Health, one of three individuals suffer from a central nervous system (CNS) disorder each year, constituting more than 20% of total health care spending in the United States. The brain is the center for a wide spectrum of psychiatric, neurologic, and or neurodegenerative disorders yet there are no effective treatments for the majority of brain disorders. Neuropeptides present themselves as attractive drug candidates due to their enhanced potency and low toxicity of their metabolites. However, neuropeptides are not widely used to treat neurological diseases due to their limitation in targeted delivery to the brain. Two main factors prevent sufficient delivery of intact and viable peptides: low bioavailability and the presence of the blood brain barrier (BBB). It is hypothesized that chemical modifications of side chains of a small peptide will change its physiochemical properties to improve its membrane permeability and ultimately brain penetration. The goal of this project was to create a panel of compounds that represent various chemical modifications of a small peptide in the hope of improving the brain penetration.
Methods: Peptides were synthesized from C-terminus to N-terminus through acid-amide coupling. Modifications were made at the N-terminus by adding hydrophobic end groups. Structure analysis was performed by H^1-NMR.
Results: A robust platform was created for the introduction of chemical modifications to small peptides. Ten compounds have been synthesized.
Conclusion: Ten compounds have been synthesized with modifications to the parent peptide. Future plans involve screening of these compounds for their brain penetration. The results may inform rational design of prodrug chemistry to improve brain delivery of small peptides.
Acknowledgement: Anne Nguyen is the recipient of a 2018 GSK/CSPS National Undergraduate Student Research Program Award.

38. Application of Design of Experiments for Optimizing Critical Quality Attributes of Scored Controlled Released Tablet

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Purpose: The purpose of this work is to use the design of experiments (DEO) to study the influence of critical factors and their interactions on the breaking accuracy, assay, dissolution, content uniformity, and other quality attributes of the scored controlled released (CR) tablets.
Method: Scored CR tablets containing Caffeine as a model drug and Hydroxypropylmethyl-cellulose (HPMC) were prepared by direct compression using an instrumented tablet press (RoTab T, Luxner, Germany). A three-factor, two-level, full factorial design was used to investigate the effect of hardness, scoring line (one side vs two sides) and deepness of the scoring line, on quality attributes of the scored CR tablets. Tablet hardness was measured using a hardness tester machine (Vector, USA), while friability was measured using a friabilator apparatus (Sotax, USA). Assay and content uniformity were determined on 10 tablets using a UV-spectroscopy technique. Dissolution test was evaluated using a USP dissolution apparatus type II at 50 rpm in phosphate buffer pH 6.8.
Results: Splitting of CR tablet generates higher weight variability as compared to the whole CR tablets. Tablets with 2 deep scoring lines are easy to break and show a good breaking accuracy compared to one scoring line tablets. Assay and dissolution profile of splits tablets (2 deep scoring lines) were not significantly different compared to the whole tablets, at high compression force (high hardness).
Conclusion: Formulation composition, process manufacturing and other physical characteristics

have greater influence on the accuracy and quality attribute of scored CR tablets.

39. Bisphosphonate Drug Alveolar Bone Burden in Osteoporosis

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Purpose: Osteonecrosis of the jaw (ONJ), a severe bone disorder that leads to bone death is caused mainly by nitrogen-containing bisphosphonate drugs. Recent observations suggest that the nature of ONJ is not an area of avascular necrosis, nor an osteomyelitis, but an inability of the alveolar bone to respond to injury. Our study hypothesis was that the identification of new metabolites involved with the pathogenesis of ONJ may serve as a diagnostic mechanism for measuring the extent of ONJ present in the bones of patients following long-term bisphosphonate therapy. We used a metabolomics profiling approach, to observe metabolic changes in plasma and urine in an established rat model of osteoporosis. The commercially available Biocrates kit was used as a tool in order to provide new information on the alteration in metabolite level and to determine the potential therapeutic insight offered by metabolomics profiling following bisphosphonate drug intervention.
Methods: The study subjects were divided into four experimental groups: control rats dosed with vehicle, rats dosed with 0.12mg/kg Alendronate twice Weekly, third group dosed with active vitamin D (100ng/kg) and a combination group receiving both Alendronate and vitamin D. Plasma and urine from the four groups of rats were collected at baseline, 4 week and 8 week study endpoint and subjected to metabolomic analysis and *in vivo* Micro CT scan measurement of bone volume.
Results: Preliminary results by micro-CT confirmed an osteopenic phenotype developing in the trabecular bone of all OVX rats. A distinct metabolite "fingerprint" was measured following drug treatment between control and treated groups, with key metabolites detected in Alendronate-dosed groups compared to the other groups.
Conclusions: These findings suggest that the use of a metabolomic approach would be of value to dentists attempting to alleviate symptoms associated with osteonecrosis of the jaw induced by bisphosphonate drug therapy.

Pharmaceutical & Analytical Chemistry

40. Lipid based Liposomal Formulation of Phytosterols and Tocopherols into Functional Food

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Purpose: Phytosterols and tocopherols, extracted from canola oil waste stream can be a component of functional foods. They have cholesterol lowering abilities and antioxidant properties. However, their lipophilic nature as well as heat and light sensitivity makes it challenging to incorporate them into functional food. The aim of this study is to develop bifunctional liposomes of phytosterols and tocopherols and integrate them into functional food.
Method: Liposomes containing phytosterols and tocopherols were creating using three different approaches: homogenization, ultrasonication and heating methods. Liquid chromatography- tandem mass spectrometry (LC-MS/MS) quantitative method was developed and validated to determine the incorporation efficiency of phytosterols and tocopherols into liposomes.
Results: The particle size was significantly larger when employing the heating method (258nm) compared to homogenization (192nm) and ultrasonication (195nm) method. Whereas zeta potential were comparable among the three formulations (-15mn to -18mv). Linearity (R^2= 0.998) and adequate sensitivity (0.005µg/ml) was achieved by quantitation method. In addition, the method was validated as per the FDA guideline, ensuring robustness of analytical platform. Incorporation efficiency of the phytosterols and tocopherols was around 95% with homogenization method.
Conclusion: All three-formulation strategies showed size and zeta potential suitable for colloidal stability and oral drug delivery. Robust analytical method was developed and validated and applied to measure incorporation efficiency. The optimized liposomes will be incorporated into orange juice. Formulation stability in pasteurized orange juice will

be evaluated for 60 days.

41. The Quantitative Analysis of Titanium Dioxide in Commonly used Sunscreen Cosmetics by Ultraviolet-visible Spectroscopy

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Purpose: Frequent exposure to UV radiation has pronounced harmful effects on human health. To prevent skin damage from the sun's radiation, many skin care products, such as moisturizing creams, body sprays, lipsticks, makeup foundations, and face lotions contain titanium dioxide as sunscreen to block UV radiation. The Industrial Pharmaceutical Laboratories Division at the Toronto facility of Alpha Healthcare has developed and validated a simple and sensitive method for the determination of Titanium Dioxide in human Sunscreen Lotion by Ultraviolet Visible spectrophotometer (UV/VIS).
Methods: 2.0 g of sample was weighed on an Ash-less filter paper (70 mm) and placed in an 800 mL Kjeldahl flask. To this, 6 g of Ammonium Sulphate and 30 mL of Sulphuric Acid was added. The mixture was heated gently on an electric heater until the sample was completely carbonized. The mixture was then heated at a higher temperature (400C) until the sample was yellowish or brown in color. The sample was let cool, added 200 mL of water, quantitatively transferred the contents into a 500 mL volumetric flask and diluted to volume with water. The solution was filtered through Whatman #4 filter paper. Three calibration standards and one blank sample were also prepared simultaneously using the same method. The absorbance of sample, standards and blank was measured at Wavelength 410 nm using 1 cm cuvette cell by Perkin Elmer LAMBDA 25, UV / VIS spectrophotometer.
Results: The method produces acceptable linearity (r^2= more than 0.999) precision (CV= less than 2%) and accuracy (recovery= 100$\pm$2.0%) to a minimum concentration of 30 microgram per mg in human sunscreen lotion.
Conclusion: The method is very simple, rugged, and convenient. It can be used to analyze titanium dioxide in human sunscreen lotion with no observable matrix interferences.

42. FOXM1 Inhibitors: A Structural Activity Relationship Study

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Purpose: The FOrkhead boX M1 (FOXM1) is a transcription factor essential for normal activation of the cell cycle and replication. However, increasing evidence links its overexpression with cancer development, poor prognosis and drug resistance which makes it an interesting drug target. Based on a previously performed molecular modeling and molecular dynamics simulations, we hypothesised that the current FOXM1 inhibitor (FDI-6) binds to the FOXM1 DNA binding domain mainly by forming a pi-sulfur interaction and a Halogen bonding with its 4-fluorophenyl to the ARG287 of the FOXM1 DNA binding domain.
Method: To test this hypothesis, we employed FDI-6 as a scaffold, to synthesize different derivatives by removing or replacing different groups at 4-fluoro phenyl position. We used the MTT method to compare the cytotoxicity level of the synthesized compounds with the FDI-6 (**7c**) in two FOXM1 expressing cell lines (MDA-MB-231 and MCF-7). Next, we determined the level of nuclear FOXM1 expression on triple negative breast cancer cell line (MDA-MB-231) followed by making the recombinant FOXM1-DBD to perform ElectroMobility Shift Assay (EMSA).
Results: The experimental results provide evidence supporting the hypothesis describing an essential halogen-Arg297 binding interaction exerted by the FOXM1 inhibitor. The biological evaluation of drug molecules, especially the measurement of nuclear FOXM1 levels in MDA-MB-231 triple negative breast cancer cells line and EMSA, are in accordance with theoretical (calculated) binding free energy calculations, showing the importance of this halogen-Arg297 interaction in the overall compounds suppressing ability.
Conclusion: We hope that the results presented in this investigation provide essential insights to elucidate the mechanism of action exerted by FOXM1 inhibitors at this protein's DNA binding domain. Finally, we also propose that these structural requirements may be used to design (future) more potent and selective FOXM1 inhibitors in Medicinal Chemistry.

Pharmacokinetics & Pharmacodynamics

43. Assessing Cardiovascular Toxicity of Doxorubicin and Isoproterenol by Hemodynamics and *in vivo* Catabolism of Adenosine 5-'triphosphate

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Purpose: Previous studies have shown catabolism of adenosine 5'-triphosphate (ATP) in systemic blood is a potential surrogate biomarker for cardiovascular toxicity. We compare the acute toxicity of high dose of doxorubicin (DOX) and isoproterenol (ISO) on hemodynamics and ATP catabolism in circulation.
Method: Sprague Dawley (SD) rats were each given either a single dose of 30 mg/kg ISO, or twice daily dose of 10 mg/kg of DOX or normal saline (control) for 4 doses by subcutaneous injection. Blood samples were collected up to 6 hours for measuring concentrations of ATP and its catabolites. Hemodynmics was recorded continuously. Difference was considered significant at $p < 0.05$ (ANOVA).
Results: Mortality was 1/8, 5/11 and 0/11 for the DOX, ISO and control groups, respectively. Systolic blood pressure was significantly lower in the DOX and ISO treated rats than in the control measured at the last recorded time (76 ± 9 for DOX vs 42 ± 8 for ISO vs 103 ± 5 mmHg, $p < 0.05$ for all). Blood pressure fell gradually after the final injection for both DOX and control groups, but abruptly after ISO followed by a rebound and then gradual decline till the end of the experiment. Heart rate was significantly higher after ISO, but no difference between the DOX and control rats ($p > 0.05$). RBC concentrations of ADP and AMP, and plasma concentrations of adenosine and uric acid were significantly higher in the ISO group. In contrast, hypoxanthine concentrations were significantly higher in the DOX treated group ($p < 0.05$).
Conclusion: Acute cardiovascular toxicity induced by DOX and ISO may be measured by changes in hemodynamics and breakdown of ATP and adenosine in the circulation albeit a notable qualitative and quantitative difference was observed (supported in part by funding from Dalhousie Faculty of Health and Pharmacy Endowment Foundation).

44. Effects of Tacrolimus on Mycophenolic Acid Exposure in *de novo*, Steroid-Free Adult Kidney Transplant Patients

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Purpose: Mycophenolic acid (MPA) is commonly dosed empirically in combination with tacrolimus (FK), with or without corticosteroids, for the prevention of graft rejection in transplant recipients. FK has been known to decrease the intrinsic clearance of MPA in various *in vitro* models, but conflicting clinical drug-drug interaction data have been reported. Because the majority of MPA pharmacokinetic and drug interaction studies have been conducted in subjects on steroid-based pharmacotherapy, we hypothesized that FK can affect the exposure of MPA in adult kidney transplant patients on *steroid-free* regimens.
Methods: Open label, prospective, observational cohort study involving patients (N=49) on steroid-free MPA/FK. The following clinical variables were collected: sex, age, weight, height, body surface area (BSA), serum creatinine (SrCr), albumin, and FK/MPA concentrations. MPA and FK exposures (area under the concentration-time curve, AUC) were calculated using the trapezoidal rule or limited sampling strategies, depending on data sampling intensity.
Results: Parameter values were: sex (N=27 females), age (50±13 years, mean±SD), weight (71.8±18.2 kg), height (166.9±9.7 cm), BSA (1.82±0.26 m^2), SrCr (1.2±0.3 mg/dL), albumin (4.0±0.5 g/dL), FK trough concentration/dose (1.46±0.72 µg/L/mg), FK exposure/dose (25.0±14.4 µg·h/L/mg), MPA dose (1.62±0.50 g/day) and MPA exposure/dose (25.3±11.0 mg·h/L/g). Using log-transformed data, initial simple linear regression analyses indicated that MPA exposure was only

associated with "weight", "BSA", and "MPA daily dose". Stepwise multiple regression models, using various combinations of clinically relevant variables, identified "BSA" and "MPA daily dose", but not "FK AUC", as predictors of MPA exposure. Moreover, when patients were sub-categorized based on FK AUC or post-transplant time (where < 1 year was associated with higher FK AUC), no significant differences in MPA exposure were observed.
Conclusion: Our novel findings indicate that a clinically significant drug-drug interaction between FK and MPA was not clearly evident in this patient population. Further analyses using non-linear mixed-effects modeling are ongoing.

45. Comparison of Population PK and Non-compartmental Analyses for Tailoring PK in Hemophilia A with Limited Sampling

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Purpose: Hemophilia A is a bleeding disorder characterized by the deficiency of coagulation factor VIII. Standard treatment to prevent bleeds aims at infusing the patient with the missing factor to target a trough FVIII level above 1%. Individual pharmacokinetic (PK) estimation is essential to tailor treatment and usually performed by blood sampling and non-compartmental analysis (NCA). NCA requires many blood samples whereas population pharmacokinetic (popPK) modelling requires fewer samples and might be better suited to this task. The objective was to assess if a popPK model provides equivalent PK estimates to NCA with limited samples.
Methods: A virtual dataset was created with 1000 subjects having observations at predose, 1,3,6,12,24,48 and 72h post infusion (rich data) based on a popPK model [1]. PK parameters were estimated and compared between NCA and Bayesian forecasting from the popPK model. Data subsets having only 3 observations (sparse data) were also compared.
Results: Comparison between the methods using on rich data led to a 7% median error and R^2 of 0.68 for half-life. Using sparse data at predose, 48 and 72h or predose, 1 and 48h led to a median error lower than 10% and R^2 higher than 0.62. Similar results were obtained with other PK parameters.
Conclusion: The correlation between PopPK model and NCA outcomes using rich or sparse data was similar. Therefore, PopPK models are well suited for individual PK estimation with few observations and limited sampling analysis is a useful diagnostic tool that assesses the efficiency of limited sampling strategies.
[1] Zhang Y, Roberts J, Tortorici M, Veldman A, St Ledger K, Feussner A, Sidhu J. Population pharmacokinetics of recombinant coagulation factor VIII-SingleChain in patients with severe hemophilia A. J Thromb Haemost 2017; 15: 1106–14

46. Impact of Inflammation on the Expression of Renal Drug Transporters in Pregnancy

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Purpose: To examine the impact of viral-induced inflammation on key drug transporters in the kidney. Pregnant women are frequently exposed to viral infections including cytomegalovirus, herpes simplex, HIV, and hepatitis. These patients are on antiretroviral medications, many of which are excreted renally. It is well known that infection and inflammation impose changes in the expression and activity of drug transporters in several tissues which can lead to altered drug disposition. However, there is scarcity of knowledge about the effect of inflammatory stimuli on renal drug transporters.
Methods: Pregnant Sprague-Dawley rats received single intraperitoneal doses of viral mimetic polyinosinic/polycytidylic acid [poly(I:C)] (5.0 mg/kg) or saline at gestation day 18 (n = 8/group). Kidneys were collected 24 h later. mRNA and protein expression of transporters were measured using quantitative RT PCR and Western blot.
Results: As compared to saline controls, Mrp2, Bcrp, Octn1, Oat1, Oat2, Oat3, Urat and Oatp4c1 mRNA levels were downregulated by 38-52% ($p < 0.05$) and the transcript level of Ent1 was increased by 75%. While protein expression of Bcrp, Urat1 and Pept2 were significantly reduced, decreases in Mrp2, Oat2 and Oat3 protein expression did not reach significance. Transcript levels of Mdr1a, Mdr1b, Mrp4, Oct1, Oct2, Oct3, Octn2, Mate1, Ent2 and Pept1 were unchanged.
Conclusion: Viral-induced inflammation mediates significant changes in the expression of several key

drug transporters in the kidney of pregnant rats. Many clinically important endogenous and exogenous compounds are substrates of these transporters, therefore, inflammation-mediated alterations in transporter expression could affect their maternal disposition and fetal exposure.

47. The Impact of Diet Induced Obesity on the Microsomal Glucuronidation of Propofol in Rats

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Purpose: To investigate the functional changes in glucuronidation caused by diet-induced weight gain using the commonly used anesthetic/sedative agent, propofol. Propofol is a known substrate for glucuronidation.
Methods: Liver microsomes were harvested from male Sprague–Dawley rats given for 14 weeks either normal rodent chow with water (controls); normal chow and high fructose corn syrup water (HFCS); 45% high fat diet (HF) chow with water; or a combination of HFCS and HF. Propofol was incubated with the microsomal protein in incubation media (microsomal protein, UDPGA, $MgCl_2$ in phosphate buffer). A range of propofol concentrations (5 - 1000 μM) was used. After 10 min, the reaction was stopped by the addition of acetonitrile and the tubes were centrifuged to remove protein. HPLC was used to assay propofol remaining in the solution.
Results: Each of the groups fitted well to the simple Michaelis-Menten relationship except for the HFCS group, which had a very different profile that fit best to a one enzyme system with a shape factor. For the other groups, the HF treated rats had the lowest measures of Vmax and CLint (the ratio of Vmax to km). We also compared the velocity of formation of glucuronidated propofol at the highest concentration of 1000 μM for all groups. In that comparison, the data indicated that for the HFCS treated animals, there was a higher rate of formation of the glucuronide metabolite than other groups.
Conclusions: Diet-induced obesity was associated with a general reduction in the hepatic microsomal rate of glucuronidation of propofol when fat alone was incorporated into the diet. Interestingly, the kinetics in rats given HFCS alone or in combination with fat appeared to have a higher rate of glucuronidation based on Vmax, and when given as HFCS without fat, a profound change in the kinetic profile of glucuronide formation.

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48. Using the Wet Bridge Transfer System to Assess Exogenous Surfactant as a Pulmonary Drug Delivery Vehicle

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Background: Due to its complex branching structure, drug delivery to the remote areas of the lung is a major challenge. Consequently, most therapies, such as those treating pulmonary infection and inflammation, utilize large systemic dosing, with the potential for adverse side effects. A novel alternative strategy is to use exogenous surfactant, a material capable of distributing throughout the lung, as a pulmonary drug delivery vehicle.
Objectives: Utilize an *in vitro* transferring system to assess exogenous surfactant (BLES) as a pulmonary drug delivery vehicle.
Methods: An *in vitro* technique was developed to simultaneously study surfactant delivery and drug efficacy. This Wet Bridge Transfer system consisted of two connected wells in which drugs were instilled into an administration well and function was tested in a remote well. The distal wells were seeded with either bacteria or stimulated macrophages. Then therapeutics were administered to the delivery well alone or in combination with BLES. Outcomes involved spot plating for bacterial killing and cytokine analysis for anti-inflammatory effects.
Results: Administering any of the antimicrobial or anti-inflammatory drugs alone to the delivery well elicited no change for outcomes in the remote well. However, bacterial growth in the remote well was reduced by several BLES/antibiotic preparations and a few BLES/anti-inflammatory mixtures lowered its pro-inflammatory cytokine concentrations.
Conclusions: The Wet Bridge Transfer system can be used to rapidly assess and screen surfactant-based therapies prior to their assessment *in vivo*. Furthermore, our results indicated that exogenous surfactant was an effective delivery vehicle for many antimicrobial and anti-inflammatory therapeutics.
Keywords: Surfactant, Drug Delivery, Bacterial Infection, Inflammation, Wet Bridge Transfer System

49. Gene Expression of Solute Carrier Transporters in Multidrug Resistant Breast Cancer Cells

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Background: Jadomycins are natural products that retain their cytotoxic properties in multi-drug resistant (MDR) breast cancer cells by avoiding efflux through ATP-binding cassette (ABC) efflux transporters. It is necessary to understand jadomycins' cellular uptake mechanisms in order to better utilize these compounds. We hypothesize that solute carrier organic anion (SLCO) transporters are responsible for jadomycin uptake; therefore, the gene expression of these transporters must be evaluated in breast cancer cells.
Objectives: To evaluate the gene expression of 11 SLCO transporters in a panel of breast cancer cell subtypes.
Methods: The mRNA expression of 11 SLCOs was quantified using quantitative polymerase chain reaction (qPCR) in drug sensitive MCF7-CON and taxol-, etoposide-, and mitoxantrone- resistant MCF7 breast cancer cells which overexpress ABCB1, ABCC1, and ABCG2 efflux transporters, respectively. Comparisons were also made between BT474, SKBR3, and MDA-MB-231 breast cancer cell lines and non-cancerous MCF-10A breast epithelial cells.
Results: *SLCO4A1* and *3A1* were expressed significantly higher than other transporter genes in drug resistant MCF7 cells. There was significantly higher expression of *SLCO4A1* compared to several other transporters in MCF-10A cells and SKBR3

cells; and *SLCO1C1* compared to several other transporters in MCF7-CON cells. There were no significant differences when comparing the transporters in BT474 and MDA-MB-231 cell lines.
Conclusions: *SLCO4A1* and *3A1* were expressed at significantly higher levels versus the other transporter genes in MDR MCF7 cells. These transporters could serve as a conserved transport mechanism for intracellular delivery of anti-cancer drugs, suggesting they may be responsible for the cellular uptake of jadomycins.
Keywords: Breast cancer, multi-drug resistance, jadomycins, solute carrier organic anion transporters.

50. Gene-specific Epigenetic Modifications May Contribute to Postnatal Neurodevelopmental Deficits in OGG1 KO Mice Exposed to Ethanol *in utero*

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Background: Oxidative DNA damage and epigenetic changes occur in the brains of children exposed to ethanol (**EtOH**) *in utero.* We previously reported that reactive oxygen species-initiated DNA damage in fetal brains, and postnatal learning and memory deficits were enhanced in EtOH-exposed oxoguanine glycosylase 1 (*Ogg1*) -/- knockout (KO) progeny, which cannot repair the pathogenic DNA lesion 8-oxo-2'-deoxyguanosine (8-oxodG).
Objectives: We are investigating the role of 8-oxodG-dependent epigenetic changes in the mechanism of EtOH-enhanced postnatal neurodevelopmental abnormalities in *Ogg1* KO mice.
Methods: Global DNA 5-methylcytosine (5-mC) levels, mRNA expression of *Esr1* involved in learning and memory formation, and the association of histone marks with the *Esr1* gene promoter via ChIP-qPCR, were measured in saline- or EtOH-exposed (2 g/kg single i.p.) fetal brains extracted 6 and 24 h post maternal treatment on gestational day 17.
Results: 5-mC was increased by 50% in saline-exposed *Ogg1* -/- fetal brains ($p<0.05$) at 24 h. A similar non-significant trend occurred in EtOH-exposed fetal brains. *Esr1* expression was increased in fetal brains of EtOH-exposed *Ogg1* -/- vs +/+ progeny at 6 and 24 h ($p<0.05$), and compared to saline-exposed *Ogg1* -/- progeny at 24 h ($p<0.01$). An increased association of the repressive mark H3K27me3 occurred in EtOH- vs saline-exposed *Ogg1* +/+ progeny ($p<0.05$), with a similar non-significant trend in *Ogg1* -/- fetal brains.
Conclusions: The DNA lesion 8-oxodG and/or lack of OGG1 results in epigenetic changes that may contribute to the neurodevelopmental abnormalities seen in *Ogg1* KO progeny (Support: CIHR, UofT Faculty of Pharmacy)
Keywords: DNA oxidation, Epigenetics, Estrogen Receptor, Ethanol, FASD

51. An Investigation into T-cell-mediated Drug Hypersensitivity Reactions

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Background: Delayed drug hypersensitivity reactions (DHRs) are T-cell-mediated idiosyncratic reactions that can erupt days to weeks after initial drug exposure. Many drugs can cause these reactions that commonly presenting in skin. Previous research into the pathophysiology often groups clinical presentations together, however there is some evidence suggesting that cutaneous reactions have different T-cell subset involvement, and therefore different underlying mechanisms.
Objective: Our objective is to address this issue, and determine pathophysiology in context of drug type and resulting clinical presentation.
Methods: Peripheral blood mononuclear cells (PBMCs) are isolated from peripheral blood of patients with confirmed drug allergy and healthy controls, and stimulated with the culprit drug in presence of autologous dendritic cells. T-cell subsets are assessed by measuring surface markers, and secreted effector cytokines using flow cytometry,

ELISA and ELISpot techniques. Autologous dendritic cells will be derived from monocytes. A biobank of isolated PBMCs from affected patients and healthy controls will be generated.
Results: Preliminary results include optimizing proliferation and staining of isolated lymphocytes and different techniques to generate autologous dendritic cells. Tritiated thymidine (H^3) for measuring T-cell proliferation and percoll method for isolation of monocytes have provided satisfactory results. It is anticipated that different clinical presentations occur due to response of different T-cell subsets and effector cytokines.
Conclusions: This study will provide insight into the underlying pathophysiology of DHRs while aiming at developing reliable tests for prediction and diagnosis. We aim to help lessen patient suffering and associated healthcare costs, by improving accurate prediction and early diagnosis of DHRs.
Keywords: Drug; Hypersensitivity; Skin; Flow cytometry; T-cell

52. The Role of the Dopamine D3 Receptor in Alcohol Use Disorder

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Background: While animal models have implicated the dopamine D3 receptor (D3R) in alcohol use, AUD research in humans provides limited understanding with respect to the specific role of D3R in AUD. This project aims to extend on preclinical research by investigating D3R in human AUD subjects.
Objectives: 1. to examine the regulation of D3R levels in AUD subjects (compared to previously acquired controls); and 2. to explore how craving and motivation to consume alcohol relate to D3R levels. We hypothesize an upregulation of D3R in AUD subjects as well as a positive association between D3R levels and our behavioral measures.
Methods: D3R levels in AUD subjects (n=10) (and healthy controls, n=18) were estimated using Positron Emission Tomography (PET) along with a D3R preferring radiotracer, [^{11}C]-(+)-PHNO. D3R levels in the AUD group were then correlated with measures of craving (assessed by a cue-exposure paradigm) and motivation to consume alcohol (assessed by a computer-assisted intravenous alcohol self-administration paradigm under a progressive ratio schedule).
Results: Preliminary data show no differences in [^{11}C]-(+)-PHNO binding between AUD subjects and controls. Exploratory analyses in the AUD group revealed no relationship between self-administration peak blood alcohol concentration and [^{11}C]-(+)-PHNO binding. However, there was a positive association between craving score increases and [^{11}C]-(+)-PHNO binding in several brain regions (e.g., globus pallidus, $r=0.74$, $p<0.05$; dorsal striatum, $r=0.89$, $p<0.001$; ventral striatum, $r=0.75$, $p<0.05$).
Conclusions: While these data show no differences in D3R binding between AUD subjects and controls, this early data does suggest a role of D2/3R in alcohol craving.
Keywords: Dopamine, PET, PHNO, AUD, D3

53. BRCA1 Protects the Embryo from Oxidative DNA Damage in *Brca1* Knockout Mice

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Background: Although primarily associated with cancer, the breast cancer 1 (*Brca1*) gene also provides embryoprotection from reactive oxygen species (ROS). *Brca1* regulates important cellular pathways, including DNA repair, and the homozygous knockout (KO) is embryolethal. However, heterozygous (+/-) progeny are thought to develop normally.
Objectives: (1) Characterize the level of BRCA1 protein deficiency in +/- *Brca1* KO embryos vs. wild-type (+/+) littermates and adult brain; and, (2) determine if KO embryos exhibit enhanced DNA damage with or without *in utero* exposure to the ROS-enhancer ethanol (EtOH).
Methods: +/- *Brca1* KOs were mated, and pregnant dams were either untreated or treated on gestational day (GD) 12 with EtOH (4 g/kg i.p.) or saline. Embryos were collected 6 hours later. BRCA1 protein was measured in untreated embryos via western blot. Treated embryos were assessed by ELISA for the DNA lesion 8-OH-2'-

deoxyguanosine, and by western blot for γH2AX, indicating DNA double strand breaks.
Results: BRCA1 levels were reduced by 58% in *Brca1* +/- embryos vs. +/+ littermates ($p<0.0001$), and by a lesser 38% in +/- adult brains compared to +/+ brains ($p<0.05$). DNA damage was increased in saline-exposed +/- embryos vs. +/+ littermates ($p<0.05$), and was exacerbated by EtOH exposure ($p<0.01$).
Conclusions: Modest BRCA1 deficiencies of either genetic or epigenetic origins may constitute a risk factor for abnormal development, suggesting a role for BRCA1 beyond cancer. These results may be relevant to autism spectrum disorders (ASD) and fetal alcohol spectrum disorders (FASD). (Support: CIHR, Faculty of Pharmacy)
Keywords: Breast cancer 1, BRCA1, DNA damage, DNA repair, teratogenesis, autism spectrum disorders, ethanol, fetal alcohol spectrum disorders

54. The Effects of War Stress on Pregnancy Outcomes During the Conflict in Tripoli, Libya

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Background: Prolonged, severe stress is unhealthy for pregnancy. There are limited studies evaluating the potential adverse effects of war on pregnancy outcomes. On February 17, 2011, a civil conflict erupted in Libya. Major stress factors in Tripoli during the war were: bombing of the military centers in the city and low quality of life. However, there was no destruction of medical buildings. Updated health records were investigated to determine the effect of war stress on pregnancy outcomes.
Objective: The objective of this study is to investigate the influence of war on pregnancy outcomes during the 2011 conflict in Tripoli, Libya.
Methods: All the neonatal records that were admitted to the neonatal intensive care unit at the Archives Department at the Tripoli Medical Center for the period covering 2009, 2010 and 2011 were reviewed. The following data was collected: date of admission, gestational age, days in hospital, diagnosis with congenital heart defect (CHD) and causes of death.
Results: No statistical difference between the years on the rates of prematurity and infant death. However, there was statistical higher rate of CHD in 2011 (the war year) and statistical lower rates in multiple births comparing to the previous two years (2009 and 2010).
Conclusions: Based on these results war stress may increase the rate of CHD. While multiple births is a major risk factors for prematurity and this was reduced in the war year the results may suggest the cause of prematurity was due to war stress. More research is needed to further evaluate if any relationship truly exists.
Keywords: Stress, Pregnancy Outcome, Congenital Heart Defect

55. Optimizing Chronic Hepatitis C Treatment in a Canadian Cohort

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Background: Chronic Hepatitis C virus (HCV) infection is a major cause of cirrhosis and liver disease, making it a leading indicator for liver transplantation. In the era of direct acting antiviral therapy, ribavirin is still used to improve outcomes for difficult to treat patients and shorten therapy length. However, ribavirin can cause serious anemia, requiring dose reductions to prevent further harm to the patient. This can compromise treatment success, resulting in longer treatment periods and higher costs.
Objectives: We aim to validate previously identified genomic variants, and discover novel variants associated with ribavirin-induced anemia in Canadian patients and develop a pharmacogenomic

prediction model to identify patients most likely to develop anemia.
Methods: We have recruited patients treated for chronic HCV infection across Canada and genotyped them for ~700,000 variants across the genome. A genome-wide association study will be conducted to uncover novel genomic predictors of ribavirin-induced anemia by adjusting for significant associations with previously identified variants.
Results: Currently, we have recruited 189 patients who have completed ribavirin-containing therapy. Of these, 67 developed clinically diagnosed anemia, with a median hemoglobin decline of 35.5g/L and an increased likelihood of having lower baseline hemoglobin levels.
Conclusions: Knowing in whom serious anemia to ribavirin is likely to occur via precision medicine approaches will allow for tailoring of therapy to individual patients. This will therefore increase the probability of treatment success and minimize the likelihood of anemia, all which would decrease both economic and psychological burdens on affected families.
Keywords: Hepatitis C, ribavirin, anemia, pharmacogenomics

56. Towards Reducing the Burden of Hepatitis C-related Complications through Genomics-guided Treatment Optimization

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Background: The World Health Organization has identified viral hepatitis as a public health threat, with an estimated 71 million people living with chronic hepatitis C infection globally. In 2015, approximately 400,000 deaths globally occurred due to complications of chronic hepatitis C infection. A new wave of highly effective drugs, collectively called direct acting antivirals (DAAs), promise the elimination of hepatitis C-related complications with reported cure rates over 95%, yet these rates may not adequately represent real-world patients with difficult-to-cure infections.
Objectives: Genomic differences influence the likelihood of curing hepatitis C, and we aim to uncover genomic predictors of treatment failure associated with these new DAAs. These predictors can be used to further improve cure rates through genomics-informed treatment optimization.
Methods: Given that sofosbuvir is the most commonly used DAA in Canada, we have recruited patients treated with sofosbuvir-containing regimens from five Canadian sites. We are collecting comprehensive clinical and genomic data, which will be used in logistic regression analyses to uncover genomic predictors of sofosbuvir-based treatment failure.
Results: We have recruited 380 patients treated with sofosbuvir-containing regimens. Of the 226 patients who have completed therapy, 22 failed to eradicate the hepatitis C virus, representing a cure rate of only 90% in our real-world cohort. Genomic DNA from the patients has been extracted and is available for high-throughput genotyping.
Conclusions: Understanding how genomic differences contribute to failure of DAA-based regimens could lead to personalized treatment decisions and a reduced burden of hepatitis C-related complications.
Keywords: Hepatitis C, genomics, sofosbuvir, treatment failure

57. Targeting Metabotropic Glutamate Receptor 5 (mGluR5) Ameliorates Huntington's and Alzheimer's Disease Pathology via Activating Conserved Mechanisms of Autophagy

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Background: Huntington's disease (HD) and Alzheimer's disease (AD) are neurodegenerative

disorders that are characterized by progressive accumulation of proteotoxic aggregates, mutant huntingtin in HD and amyloid β in AD. Genetic deletion of mGluR5 reduced disease pathology in HD and AD by enhancing the clearance of proteotoxic aggregates via a mechanism that was not described. Pharmacological blockade of mGluR5 had favorable outcomes in AD mice.

Objectives: We tested whether the inhibition of mGluR5 will be effective in delaying the progression HD by activating the autophagy and whether this autophagic clearance of aggregates mechanism is conserved in AD.

Methods: zQ175 HD, APPSwe/PSEN1dE9 and 3xTg-AD mice were treated with the highly specific mGluR5 negative allosteric modulator CTEP for 12 weeks. zQ175 mice were assessed for changes in motor and cognitive function. Autophagy markers were assessed in brain slices and lysates from HD and AD mice.

Results: CTEP improved in grip strength, latency on rotarod, novel object recognition scores and % error in limb placement during ladder task in zQ175 mice. This was paralleled by an enhanced clearance of huntingtin aggregates and a GSK3β-dependent degradation of ZBTB16 and stabilization of the autophagy adaptor ATG14. CTEP also activated ULK1 resulting in phosphorylation and activation of the autophagy adaptor ATG13. Interestingly, CTEP activated similar pathway in APPSwe/PSEN1dE9 and 3xTg-AD mice.

Conclusions: we provided the first description of mGluR5 signaling via a conserved autophagic mechanism in two neurodegenerative diseases. Our findings indicate that mGluR5 negative allosteric modulators can be repurposed clinically to improve HD and AD progression.

Keywords: mGluR5, Autophagy, Huntington's disease, Alzheimer's disease, ZBTB16

58. Aldehyde Dehydrogenase – A Real Pharmacogenomic and Toxicogenomic Crossroad

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Background: The xenobiotic response may be influenced by polymorphic metabolizing enzymes. We previously reported [1] important pharmacogenetics differences among Pakistani breast cancer patients and compared them with allele frequencies in Africa, China, Europe, North America, and other regions as represented in HapMap database. Most striking difference was very high ALDH3A1 variant allele frequency. Later, we explored additional genotypes in healthy adults from different population subgroups at Karachi which remained unreported so far.

Objectives: 1. To estimate ALDH3A1 variant allele frequency among healthy Pakistanis. 2. To validate previously reported ALDH3A1 allele frequency among Pakistani breast cancer patients.

Methods: We included 155 healthy adults after informed consent and institutional approval. The DNA was extracted from saliva collected and stored in Oragene-DNA® kits. Several SNPs involved in drug metabolism and transport were genotyped. Here we present the pyrosequencing data of ALDH3A1 genotyping done at our collaborating institution (Institute of Clinical and Experimental Pharmacology, University of Kiel, Germany).

Results: The ALDH3A1 (985 C>G) variant allele frequency was 67% among our population which is significantly higher than all ethnic groups in HapMap database (Figure-1), which is similar to our previously reported 63% among Pakistani breast cancer patients. Healthy Europeans in HapMap database had lowest variant allele frequency (29%).

Conclusions: ALDH3A1 variant allele is very frequent in our population. Implications include (Figure-2) increased susceptibility of suffering from, (a) *diseases* like atherosclerosis, cancer, cataracts, infertility, neurodegeneration, (b) *hazards* related to mitochondrial dysfunction, oxidative stress, smoking, environmental pollutants, and (c) *reduced efficacy* to cyclophosphamide, nitroglyderin, tretinoin and others.

Keywords: Aldehyde dehydrogenase, Environmental hazards, Non-communicable diseases, Pharmacogenomics, Toxicogenomics

59. Development and Implementation of Pharmacogenomic Risk Prediction Models in Pediatric Oncology

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Background: Adverse drug reactions (ADRs) are increasingly recognized as important and sometimes irreversible complications of cancer treatment. Anthracyclines and cisplatin are effective chemotherapeutic agents, but their use can be limited by cardiotoxicity (anthracyclines) and ototoxicity (cisplatin) in up to 60% of patients. Genetic variants that can be used to predict who is most at risk of developing these ADRs have been discovered and replicated.
Objectives: To create pharmacogenomic risk prediction models for anthracycline and cisplatin toxicities and discuss results with oncologists to facilitate incorporation into treatment decision-making when appropriate.
Methods: Risk prediction models were developed from the linear regression of strongly-predictive genomic variants (odds ratios ≥ 3) discovered and replicated in at least three patient populations. These models were used to assess an individual patient's genomic risk of developing cardiotoxicity from anthracyclines or hearing loss from cisplatin.
Results: 241 patients have been genotyped and had their genetic risk results returned to their oncologists. The first 140 patients have been characterized to determine the impact these test results have had on their clinical care. Families and oncologists have described results as being valuable for decision-making in all cases. Additionally, for patients in the most extreme risk groups (highest and lowest risk), a change in treatment plan was ordered 30% of the time for cisplatin patients and 35% of the time for anthracycline patients.
Conclusions: Pharmacogenomic information is highly utilized in patients' treatment decisions and better informs patients about their risk of serious drug toxicity.

Keywords: Pharmacogenomics, Oncology, Precision Medicine, Adverse Drug Reactions

60. Association of Nicotine Metabolism Ratio with [^{11}C]-(+)-PHNO PET Binding in Tobacco Smokers

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Background: The rate at which nicotine is metabolized can be measured by the nicotine metabolism ratio (NMR). Fast metabolizers (FM) tend to smoke more and have a harder time quitting than slow metabolizers (SM). We have previously shown that smoking a cigarette can produce increases in DA in the ventral striatum (VS) and ventral pallidum (VP). Further, DA D2 receptors maybe down-regulated in nicotine dependence.
Objectives: The purpose of the present study was to determine whether SM and FM would have different levels of D2 and/or D3 receptor levels and different smoking-induced increases in DA in the VS and VP.
Methods: Participants (15 FM and 13 SM) underwent two PET scans with [^{11}C]-(+)-PHNO: one after 48 hours of abstinence from smoking, and the other after smoking a cigarette.
Results: D2 receptor levels were approximately 10-13% lower in SM as compared to FM during abstinence ($p=0.024$); there were no differences in D3 receptor levels. After smoking a cigarette, DA was elevated by approximately 10% in the VS ($p<0.001$) and VP ($p=0.001$) of both groups of smokers, with no differences between FM and SM.

Conclusions: Future studies will need to determine whether these changes are pre-existing or differ as a function of NMR by smoking history.
Keywords: Neuroimaging, Addiction, Nicotine

61. Careful Investigation of Pharmacogenomic Phenotypes to Uncover the Roles of *ACYP2* and *WFS1* in Cisplatin-induced Ototoxicity.

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[*] These authors jointly supervised this work

Background: Adverse drug reactions such as ototoxicity, which occurs in approximately one fifth of adult patients who receive cisplatin treatment, can incur large socio-economic burdens on testicular cancer patients who develop this cancer during early adulthood. Recent genome-wide association studies have identified genetic variants in *ACYP2* and *WFS1* that are associated with cisplatin-induced ototoxicity.
Objectives: We sought to explore the role of these genetic susceptibility factors to cisplatin-induced ototoxicity in testicular cancer patients.
Methods: Extensive clinical and demographic data were collected for 229 testicular cancer patients treated with cisplatin. Patients were genotyped for two variants, *ACYP2* rs1872328 and *WFS1* rs62283056, that have previously been associated with hearing loss in cisplatin-treated patients. Analyses were performed to investigate the association of these variants with ototoxicity in this cohort of adult testicular cancer patients.
Results: Pharmacogenomic analyses revealed that *ACYP2* rs1872328 was significantly associated with cisplatin-induced ototoxicity (P=2.83x10^{-3}, OR[95%C]:14.7[2.6-84.2]). *WFS1* rs62283056 was not significantly associated with ototoxicity caused by cisplatin (P=0.39); however, this variant was associated with hearing loss attributable to any cause (P=5.67x10^{-3}, OR[95%CI]:3.2[1.4-7.7]).
Conclusions: This study has provided the first evidence for the role of *ACYP2* rs1872328 in cisplatin-induced ototoxicity in testicular cancer patients. These results support the use of this information to guide the development of strategies to prevent cisplatin-induced ototoxicity across cancers. Further, this study has highlighted the importance of phenotypic differences in replication studies and has provided further evidence for the role of *WFS1* rs62283056 in susceptibility to hearing loss, which may be worsened by cisplatin treatment.
Keywords: *ACYP2*, cisplatin-induced ototoxicity, pharmacogenomics, testicular cancer, *WFS1*

62. Sapropterin Prevents Coronary Artery Malformations Induced by Pregestational Diabetes

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Background: Coronary artery development in the embryonic heart involves epithelial to mesenchymal transition (EMT) and cell differentiation. Hyperglycemia-induced oxidative stress can lead to the inactivation of endothelial nitric oxide synthase (eNOS), vital for heart development. Sapropterin (BH4), an antioxidant, is the co-factor for eNOS. Treatment with BH4 has been shown to improve vascular endothelial function in diabetes.
Objectives: Investigate the effect of sapropterin on embryonic coronary artery development during pregestational diabetes (PD).

Methods: Diabetes was induced by streptozotocin (50 mg/kg, IPx5) to adult female C57BL/6 mice. BH4 (10 mg/kg/day) was orally administered to pregnant mice. Fetal hearts were collected at E18.5 for coronary artery analysis and 3D reconstruction. EMT and oxidative stress were examined at E12.5 via immunostaining and qPCR. Immunoblotting determined enzyme activity.
Results: BH4 treatment to diabetic dams decreased the incidence of coronary artery malformations (CAMs) in offspring from 47.4 to 23.3%. Decreases in coronary artery luminal diameter, volume and abundance in hearts from diabetic mothers, were prevented with BH4. Diabetes reduced embryonic expression of EMT regulators , including Snail1/2 and WT1, and increased epicardial cell to cell connections, which were all reestablished to normal with BH4. Akt and eNOS activity was reduced in embryonic hearts from diabetic dams, and was returned to normal with BH4. Finally, oxidative stress was elevated in diabetic hearts and reduced with BH4.
Conclusions: Sapropterin treatment prevents CAMs induced by PD. BH4-mediated increase in Akt/eNOS activity and reduction in oxidative stress during cardiac angiogenesis provides insight into factors contributing to CAMs. BH4 may have therapeutic potential in PD.
Keywords: Sapropterin, Diabetes, Coronary Artery, Heart Development, eNOS

63. Expression of Hepatic Cytochrome P450 Drug-Metabolizing Enzymes in Diabetes and Diabetic Nephropathy

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Background: Polypharmacy, along with a high risk of adverse drug reactions, is common in diabetic patients. Many drugs are metabolized by hepatic cytochrome P450 (CYP) enzymes such as CYP3A and CYP2C. These enzymes are reduced in moderate and severe chronic kidney disease (CKD), leading to altered drug pharmacokinetics. Approximately 40% of all CKD cases are attributed to diabetic nephropathy (DN) and early DN presents as mild kidney disease. The impact of DN on CYP3A and CYP2C mediated drug metabolism is unknown.
Objectives: Evaluate the impact of diabetes and DN on expression and activity of hepatic CYP3A and 2C enzymes.
Methods: Experimental groups were given five consecutive daily 50 mg/kg injections of streptozotocin (STZ) to induce diabetes and controls were injected with sodium citrate. C57BL/6 mice were sacrificed 16 weeks following STZ and humanized CYP3A4 mice were sacrificed after 2 weeks. CYP3A and CYP2C expression was determined by real-time PCR and Western blotting. Metabolic activity of liver microsomes was assessed by measuring testosterone metabolites using LC-MS.
Results: Diabetic C57BL/6 mice showed no differences in *Cyp3a11* and *Cyp2c29* mRNA expression, and *Cyp3a11* protein expression, compared with controls. Diabetic humanized CYP3A4 mice showed no differences in CYP3A4 mRNA expression compared with controls.
Conclusions: Despite pronounced decreases in CYP expression and activity in moderate and severe CKD, diabetes or mild CKD induced by DN does not impact hepatic CYP3A or CYP2C enzyme expression. Enzymatic function, expression of transcription factors and drug transporters will be investigated in future studies using this diabetic model.
Keywords: Diabetes, diabetic nephropathy, cytochrome P450, drug metabolism

64. The Effect of Maternal Nicotine Exposure on Fetal Heart Development

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Background: Cigarette smoking during pregnancy is a risk factor for congenital heart defects (CHDs). Many women still smoke before pregnancy (25%) and during pregnancy (12%). These women resort to nicotine replacement therapies or e-cigarettes to aid in smoking cessation. Many people believe these

alternatives are safer compared to cigarette smoking, because they do not expose the fetus to the many toxins found in tobacco smoke. However, e-cigarettes contain nicotine, and the safety of nicotine on fetal heart development is not known.
Objectives: Determine if maternal nicotine exposure (MNE) during pregnancy leads to CHDs in the offspring of mice.
Methods: C57BL/6 adult female mice were treated with subcutaneous nicotine infusion at doses of 1.5 mg/kg/day via osmotic pump (Alzet #2004), a human dose equivalent to 1-10 cigarettes per day. Pumps were implanted 14 days prior to mating with a wildtype male, and nicotine exposure was continued throughout gestation. Heart samples were collected at E18.5 for morphological analysis.
Results: The incidence of CHDs in the E18.5 offspring of dams exposed to nicotine was 45.5%. The most prevalent defect observed was hypoplastic left heart syndrome (36.4%). E14.5 hearts were stained with dihydroethidium probing for superoxide, a marker for oxidative stress. Fetal hearts exposed to nicotine had significantly higher levels of ROS compared to control.
Conclusions: This research provides insight into the potential dangers of nicotine therapies during pregnancy for the developing embryo. This could decrease MNE and reduced the incidence of reproductive abnormalities such as CHDs.
Keywords: Nicotine, Cardiogenesis, Congenital Heart Defect, Developmental Biology
Oxidative Stress

65. 4-Beta Hydroxycholesterol as a Predictor of Observed Apixaban Plasma Concentration among Atrial Fibrillation Patients

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Background: Factor Xa inhibitor, apixaban, belongs to an increasingly prescribed class of direct-acting oral anticoagulants used for stroke prevention in patients with atrial fibrillation (AF). Apixaban is predominately metabolized by hepatic and intestinal cytochrome P450 3A enzymes (CYP3A4/5). To date, the relationship between apixaban blood concentrations and endogenous markers of CYP3A activity among patients taking apixaban, has not been determined. In humans, 4β-hydroxycholesterol (4β-OHC) is an endogenous oxysterol that is created through the conversion of cholesterol by CYP3A enyzmes.
Objectives: To compare plasma apixaban concentrations in AF patients in relation to their plasma 4β-OHC concentration as surrogate marker of CYP3A activity.
Methods: We determined 4β-OHC plasma concentration in 136 AF patients taking apixaban with previously determined drug plasma concentrations. Multiple linear regression analysis was used to test the relative contribution of 4β-OHC concentration to the variability in apixaban concentration while controlling for patient characteristics (age, weight, sex, serum creatinine, moderate CYP3A4/P-gp inhibitor use), *ABCG2* c.421C>A genotype, as well as apixaban dosing regimen and time since last dose.
Results: We observed a weak, inverse correlation (p = 0.016, r = -0.2063) between 4β-OHC and apixaban concentration. In our regression analysis, 4β-OHC concentration accounted for 16% of the explainable variation in apixaban concentration. Furthermore, higher apixaban concentrations were associated with increased age (p = 0.001), female sex (p = 0.002), elevated serum creatinine (p = <0.001), and amiodarone use (p = 0.024).
Conclusions: Our findings demonstrate that CYP3A activity as measured by 4β-OHC concentration is an additional determinant of apixaban plasma concentration.
Keywords: endogenous CYP3A activity biomarker, 4-beta hydroxycholesterol, apixaban, single time-point plasma concentrations

Poster Session 2

CSPS and CC-CRS

Thursday, May 24

Posters - Session 2

Thursday, May 24

Biomedical Sciences

66. Scavenger Receptor Class B Type I (SR-BI) Mediates the Cellular Uptake of CPX-351 into K562 Leukaemia Cells

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Purpose: The Scavenger Receptor class B type I (SR-BI) plays an important role in mediating the uptake of high-density lipoproteins. The purpose of this study is to assess the role of the cell surface lipoprotein receptor SR-BI in the uptake of CPX-351 liposomes (Jazz Pharmaceuticals) into K562 leukaemia cells. CPX-351 liposome formulation encapsulates a fixed ratio of daunorubicin and cytarabine, and is approved for use in acute myeloid leukaemia.
Methods: K562 cells were treated with 10nM Stealth RNAi duplexes targeting the SR-BI gene (SR-BI siRNA) or 10 nM low GC negative control Duplexes (NC), premixed with Lipofectamine RNAiMAX reagent. Cells were collected every 24 hours to determine the SR-BI gene expression levels by RT-PCR. Uptake of CPX-351 within K562 cells was determined using flow cytometry by tracking daunrobuicin. CPX-351 at concentrations of 10, 20, 30 and 50 ng daunorubicin/mL were incubated for 24, 48 or 72 hours after siRNA transfection to downregulate SR-BI. At each time point, cells were collected and analyzed at $\lambda_{ex}/\lambda_{em}$=480/590 nm on a CytoFLEX Multicolour flow instrument to determine cellular uptake of daunorubicin. Experimental data were plotted as mean±SD using GraphPad Prism (Version 5.0). Data were analyzed using two-way ANOVA with Bonferroni multiple comparisons. Significance was set at $p<0.05$.
Results: The SR-BI gene expression levels were significantly decreased by > 75% in the cells treated with 10 nM siRNA for at least 48 h, and maintained up to 120 h, compared to K562 cells treated with medium only. Uptake of daunorubicin into K562 cells treated with CPX-351 was significantly decreased in the cells where expression of SR-BI was knocked down by siRNA, compared with cells treated with NC at 24, 48, and 72 h. A 75% reduction in SR-BI gene expression (72h post siRNA transfection) resulted in a 30% reduction in CPX-351 (50ng/mL) uptake.
Conclusions: These preliminary studies suggest that SR-BI may be one potential mechanism by which CPX-351 is taken up into K562 cells.
Acknowledgements: Funding for this project was provided by Celator Pharmaceuticals Inc. prior to its acquisition by Jazz Pharmaceuticals.

67. Effects of Diet-induced Diabetes on β-cell Specific Aryl Hydrocarbon Receptor Nuclear Translocator/Hypoxia-inducible Factor-1β (ARNT/HIF-1β) Knockout Mice

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Purpose: The transcription factor ARNT/HIF1β plays a key role in maintaining pancreatic β-cell function. β-cell ARNT/HIF1β regulates glycolysis, anaplerosis, NADPH/$NADP^+$ ratio, Ca^{2+} influx and has also been shown to be one of the most down regulated transcription factors in islets from type 2 diabetic patients. Using a β-cell specific ARNT/HIF1β knockout (β-ARNT KO) mouse model, we have shown a strong role for ARNT/HIF1β in glucose sensing and insulin secretion *in vitro*. However, β-ARNT KO mice have no significant *in vivo* defects associated with glucose tolerance and insulin resistance.
Method: In order to gain a better understanding of the role of ARNT/HIF1β in the development of diabetes, we placed male β-ARNT KO mice on either a chow diet consisting of 5.5% fat or a HFD consisting of 58% fat with sucrose for 10 weeks.
Results: The only *in vivo* significant difference seen for β-ARNT KO mice on the HFD was that they had no impairment in glucose tolerance and had a significantly elevated plasma insulin during the

*ip*GTT compared to HFD fed control mice. β-ARNT KO mice had lower β-cell mass on a chow diet as compared to chow fed control mice and showed no further impairment on the HFD. Isolated β-ARNT KO islets from chow fed mice and islets from HFD fed control mice had impaired GSIS and glucose-stimulated NADPH/$NADP^+$ ratio responses as compared to control diet fed mouse islets. Isolated islets from β-ARNT KO mice on the HFD showed an improvement in GSIS and NADPH/$NADP^+$ ratio response to glucose suggesting that the defects seen in the control fed β-ARNT KO islets could be rescued by a HFD.

Conclusion: We have shown a consistent role for ARNT/HIF1β in the maintenance of β-cell function *in vitro* and β-cell mass.

68. Fluconazole Protects Against Angiotensin II-induced Cellular Hypertrophy through Inhibiting Cytochrome P450 1B1 and its Associated Arachidonic Acid Metabolites in the Heart

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Purpose: Several studies have elucidated the role of cytochrome P4501B1 (CYP1B1) and its associated arachidonic acid (AA) metabolites in the development of cardiac hypertrophy. CYP1B1 has been reported to have a major role in metabolizing AA into cardiotoxic metabolites, mid-chain hydroxyeicosatetraenoic acid (HETEs). Recently, fluconazole was shown to inhibit the formation of mid-chain HETE metabolites. Therefore, we investigated whether fluconazole confer cardioprotection against angiotensin II (Ang II)-induced cellular hypertrophy. In an attempt to determine whether similar effects will occur in vivo, we examined the effect of fluconazole on CYP1B1 and its associated AA in rats.

Methods: Rat cardiomyocytes H9c2 cells were treated with 10 μM Ang II in the absence and presence of 50 μM fluconazole for 24 hours. Also, Sprague Dawley rats (n=6) were injected intraperitoneally with a single dose of fluconazole (20 mg/kg) or saline and the heart tissues were harvested 24 hours post-treatment. Thereafter, the formation of AA metabolites was measured using liquid chromatography-electron spray ionization-mass spectrometry (LC-ESI-MS). Cardiac hypertrophic markers and CYP1B1 were determined by real time-polymerase chain reaction and Western blot analysis, respectively.

Results: Our results demonstrated that fluconazole was able to attenuate Ang-II-induced cellular hypertrophy as evidenced by a significant inhibition of hypertrophic markers, β-myosin heavy chain (MHC)/ α-MHC. The protective effect of fluconazole was associated with a significant decrease in the level of CYP1B1 enzyme and its associated mid-chain HETEs metabolites induced by Ang II. Furthermore, treatment of rats with fluconazole significantly decreased the expression of CYP1B1 enzyme and the formation level of cardiotoxic mid-chain HETEs metabolites.

Conclusion: Our results provide the first evidence that fluconazole may be repurposed as a mid-chain HETEs formation inhibitor for the treatment of cardiac hypertrophy.

69. Modeling the Dynamic Gating Mechanism and Small-molecule Binding in the $Ca_V1.2$ Channel

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Purpose: Voltage-gated calcium channels (CaVs) remain essential for normal cardiac functioning in the human body. Any abnormalities in the functioning of CaVs results in serious diseases, for example, cardiac arrhythmias and Timothy syndrome. Thus, CaVs are considered as one of the promising targets for the treatment of these diseases. Diverse types of small molecules, such as dihydropyridines and phenylalkylamine have been identified to modulate the activity of CaVs. However, their mode and site of action are still unclear. In order to understand how these drugs bind and act on the CaV, it is necessary to have a high-quality three-dimensional structure of the human CaV channel. However, this has not been resolved yet.

Methods: We have used computational molecular modeling to model the complete three-dimensional (3D) structure of the open and close CaV channel

using homology modeling and threading approach. Classical and advanced molecular dynamics simulations were carried out to explore the conformational transitions between the closed and open state. The binding orientation and critical interactions that stabilize the known modulators were identified using molecular docking and binding-free energy methods.
Results: Our molecular dynamics simulations reveal the conformational changes in the pore and voltage-sensing domains of the CaV channel. The mode-of-binding of Amlodipine, Nimodipine, and Verapamil were identified. As expected, the relative binding affinity calculations agree that both Amlodipine and Verapamil have the high potential to block the CaV channel.
Conclusion: The conformational dynamics and the interactions reported from our binding mode analysis will be useful for understanding the structure-function-dynamic relationship in the CaV channel and guiding future drug design.

70. Molecular Mechanisms of Mammalian Lignan Enterolactone in Modulating Cellular Lipid Homeostasis

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Background: Dysregulated cholesterol homeostasis is a feature of both cardiovascular disorders and cancer progression. Furthermore, dysregulated cells can exhibit elevated endoplasmic reticulum (ER) stress as an adaptive survival mechanism. A link between flaxseed lignans (FLN) anti-cholesterolemic and anti-cancer effects might exist through the ability of FLNs to modulate both ER stress and cholesterol homeostasis as FLN are known to modulate multiple targets in dysregulated cellular signaling pathways.
Purpose: This study aims to identify the molecular targets responsible for enterolacone's (ENL) ability to modulate ER stress and cholesterol homeostasis in dysregulated cell types (e.g. cancer).
Methods: Key targets involved in cholesterol metabolism, ER stress, cell survival, and vesicular cholesterol trafficking were evaluated using a battery of *in vitro* assays such as qPCR, western blot, fluorescence microscopy, gene reporter assay, and substrate uptake assay using various cell lines.
Results: A competitive binding assay, transactivation assay, and glucose uptake assay revealed ENL as a PPARϒ partial agonist. ENL modulated cholesterol and lipid metabolism targets (FASN, SREBPs, INSIG-1, LDLR, PPARϒ) and ER stress markers (ATF4, CHOP, GADD34 and GRP58). ENL reduced mitochondrial redox function and caused mitochondrial toxicity. ENL enhanced ability of select anticancer drugs (e.g: microtubule inhibitors) to decrease cell viability. Fluorescently labeled cholesterol treated cells along with ENL revealed altered intracellular vesicular trafficking linking the actin cytoskeleton.
Conclusion: A novel role may exist between the regulation of PPARϒ, lipid and cholesterol metabolism, and ER stress. These findings warrant further investigations to support FLN's ability to modulate ER stress as the key mechanism involved in the disruption of dysregulated cellular signaling. ER stress and PPARϒ mediated signaling can influence cholesterol and lipid metabolism and therefore are relevant targets in drug discovery. As well, lignans are safe and therefore are good candidates for adjuvant therapy that could improve patient longevity and quality of life.

71. DOX-Vit D, A Novel Doxorubicin Derivative, Inhibits Human Osteosarcoma Cell Proliferation by Inducing Apoptosis while Inhibiting Akt and mTOR Signaling Pathways

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Purpose: Doxorubicin (DOX) is a very potent and effective anticancer agent. However, the effectiveness of DOX in osteosarcoma is usually limited by the acquired drug resistance. Recently, Vitamin D (Vit-D) was shown to suppress the growth of many human cancer cells. Taken together, we synthesized DOX-Vit D by conjugating Vit-D to DOX in order to mitigate the chemoresistance associated with DOX. The overall objectives of the present study were to investigate the antiproliferative

and apoptogenic effects of DOX-Vit D and the possible mechanism involved in the human osteosarcoma cancer cell line, MG63 cells.
Method: For this purpose, MG63 cells were treated with 10 μM DOX or DOX-Vit D for 24 hours. Thereafter, cell proliferation, apoptotic and oxidative stress genes were determined by 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazoliumbromide (MTT) assay and real-time PCR, respectively. The protein expression level of the phosphorylated-Jun NH2-terminal kinase (p-JNK), p-p38, p-Akt and the mammalian target of rapamycin (p-mTOR) was measured using Western blot analysis.
Results: Our results showed that DOX-Vit D, but not DOX, significantly elicited apoptotic signal in MG63 cells extrinsically through a significant activation of death receptor and intrinsically by a significant induction of oxidative stress genes (heme oxygenase-1 and NAD(P)H:quinone oxidoreductase-1). Consequently, DOX-Vit D caused a significant increase in the expression of caspase-3 and BCLxs genes and thereby suppressed the growth of MG63 cells. Mechanistically, the DOX-Vit D-induced apoptogens and cell death was credited to the activation of p-JNK and p-p38 signaling pathway. This was supported by the finding that blocking of p-JNK and p-p38 significantly attenuated the DOX-Vit D-mediated apoptosis. Furthermore, the anticancer effect of DOX-Vit D against MG63 cells was mediated by inhibiting the expression of proliferative proteins, p-Akt and p-mTOR.
Conclusion: Our findings propose that DOX-Vit D suppressed the growth of MG63 cells by inducing apoptosis while inhibiting cell survival and proliferative signaling pathways.

72. Loss of Cation Channels of the TRPC Family Protects against the Development of Diabetic Retinopathy in the STZ Model and Accumulation of Reactive Metabolites

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Purpose: Diabetic retinopathy (DR) is induced by an accumulation of reactive metabolites such as ROS, RNS and RCS species, which were reported to modulate the activity of cation channels of the TRPC family. In this study, we use Trpc1/4/5/6$^{-/-}$ compound knockout mice to analyse the contribution of these TRPC proteins to diabetic retinopathy.
Methods: We used qPCR-based analysis to determine mRNA levels of TRPC channels in control and diabetic retinae and retinal cell types. Chronic hyperglycemia was induced by Streptozotocin (STZ) treatment. To assess the development of diabetic retinopathy; vasoregression, pericyte loss and thickness of individual retinal layers were analysed. Plasma and cellular methylglyoxal (MG) levels, as well as Glyoxalase 1 (GLO1) enzyme activity and protein expression, were measured in WT and Trpc1/4/5/6$^{-/-}$ cells or tissues. MG-evoked toxicity was evaluated by MTT assay.
Results: We find that Trpc1/4/5/6$^{-/-}$ mice are protected from hyperglycemia-evoked vasoregression determined by the formation of acellular capillaries and pericyte drop-out. In addition, Trpc1/4/5/6$^{-/-}$ mice are resistant to the STZ-induced reduction in retinal layer thickness. The RCS metabolite methylglyoxal, was significantly reduced in plasma and red blood cells (RBCs) of STZ-treated Trpc1/4/5/6$^{-/-}$ mice compared to controls. GLO1 is the major MG detoxifying enzyme, and its activity and protein expression were significantly elevated in Trpc1/4/5/6-deficient cells, which lead to significantly increased resistance to MG toxicity. GLO1 activity was also increased in retinal extracts from Trpc1/4/5/6$^{-/-}$ mice. The TRPCs investigated here are expressed at different levels in endothelial and glial cells of the retina.
Conclusion: The protective phenotype in diabetic

retinopathy observed in Trpc1/4/5/6$^{-/-}$ mice is suggestive of a predominant action of TRPCs in Müller cells and microglia because of their central position in the retention of a proper homoeostasis of the neurovascular unit.

73. Effect of Polyphenols on Markers of Neurodegenerative Disease

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Purpose: It is suggested that one of the main mechanisms contributing to neurodegenerative diseases (NDD) is oxidative stress, which is caused by the buildup of harmful reactive oxygen species (ROS) in the brain. Neuroinflammation is also accredited to causing many chronic NDD; when microglia are activated in response to the release of alpha-synuclein aggregates from damaged neurons, the activated microglia release inflammatory mediators. NDD are linked to glutamate-mediated excitotoxicity as well, where cells are damaged by the excessive stimulation from glutamate via inadequate uptake by glial cells. Polyphenols, found in very high levels in blueberries, are botanical nutraceuticals which have antioxidant properties and may offer protection and intervention from neurological disorders by managing ROS, reducing the inflammatory response, and providing protection in the brain from further degeneration.
Methods: Biochemical analysis was performed after the extraction of frozen wild Newfoundland berries and leaves, *Vaccinium angustiform spp*., from four different locations. We investigated the neuroprotective role of the blueberry fruits and leaves in cell cultures from mouse-pup brain dissections, and in pure cultures of rat neurons and microglia exposed to 100μM glutamate or 100ng/ml alpha-synuclein for 24-hours.
Results: It was determined that both blueberry fruits and leaves contain high levels of polyphenols, however the leaves contained significantly higher levels for all of the locations. We have also observed an increase in the number of viable cells once blueberry extract is added to cell cultures treated with 100μM glutamate or 100ng/ml alpha-synuclein.
Conclusion: The blueberry extracts have high antioxidant activity and therefore may be able to help combat oxidative stress and neuroinflammation in the brain. The blueberry extracts are also able to provide significant protection compared to controls and effectively reduce neuronal and microglial cell death, showing that their presence helps when cell death and damage is influenced by glutamate-mediated excitotoxicity or insoluble alpha-synuclein aggregates.

74. Macro- and Micro-fabrication of Chitosan Hydrogels with Anisotropic Pores for Biomedical Applications

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Purpose: The microstructure of hydrogels is composed of micro- and nano-sized pores, with random shapes, sizes and orientations. However, in several biomedical applications, it is required to adjust the pore geometry. For example, in 3D culture of neural cells, the scaffolds should contain cylindrical pores to promote directed axon regeneration. Fabrication of these non-random structures using self-assembly is a challenging task, which is still preferred over bioprinting and lithography due to biocompatibility. In this study, we exploit the self-assembly of anisotropic chitosan pores to design non-random microstructures with potential biomedical applications.
Method: The self-assembly of the anisotropic pores is triggered by diffusion of a strong base to acidic chitosan solutions, which leads to the polymer coagulation and segregation in the diffusion direction. The coagulated polymer forms a hydrogel with double pore geometry, including random nanosized pores and anisotropic micron-sized cylindrical pores. The 3D structure of hydrogel was studied using fluorescent confocal microscopy. To test the application of the anisotropic pores, the hydrogels were formed in microchannels that were made using photolithography.
Results: The dimensions and number density of the anisotropic pores were found to depend on the base and chitosan concentrations as well as the

geometrical features of the mold. The diameter of the capillaries is typically within 20-30 μm, while they can be longer than 10 mm. The hydrogel containing these capillaries shows improved NP diffusivity, measured using diffusive dynamic microscopy. Various patterns and structures of the hydrogel were formed and tested using microfluidics.
Conclusion: Chitosan hydrogels with self-assembled anisotropic pores are an interesting candidate for several biomedical applications. These hydrogels show enhanced diffusive properties that can be tuned by modifying the pore properties. In addition, various patterns and structures that can be made using these capillaries make the gel an ideal material for tissue engineering applications.

75. Apoptotic vs. Necroptotic Cell Death Analysis in an Endothelin-1 Model of Cerebral Ischemia

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Purpose: Stroke represents one of the leading causes of long-term disability and death in North America. The failure of a majority of human clinical trials aimed at improving stroke therapy highlights the need for more defined and anatomically comparable animal models of stroke. We describe our investigations of an alternative murine model of stroke to middle cerebral artery occlusion (MCAO) which more accurately models the most common features of human clinical stroke. We also examined the relationship which two key forms of programmed cell death (apoptosis and necroptosis) play in this *in vivo* model.
Method: Induced ischemia/reperfusion in this murine stroke model is produced through the stereotactic microinjection of endothelin-1, a vasoconstrictor normally produced during acute cerebral infarct, into defined regions of the cortex. This technique is employed in both wild-type mice and those lacking caspase-3 in the presence and absence of the RIP1 kinase inhibitor Necrostatin-1 to elucidate the contribution of both apoptotic and necroptotic forms of neural injury in regions of cortical hypofusion.
Results: This endothelin-1 model demonstrates reduced infarct sizes that are geometrically defined to the cortex in a highly reproducible manner. Analysis of caspase-3 null mice further demonstrates that loss of this executioner caspase activity confers a significant protective effect against apoptotic cell death, with the region of injury reduced by more than half compared to wild-type littermates. Combinatorial inhibition of both caspase-3 and RIP1K demonstrates a still further reduction in the size of cortical injury to near vehicle-treated levels.
Conclusion: These results demonstrate that under conditions of cerebral ischemia in an improved model of cortical stroke, apoptotic and necroptotic forms of programmed cell death constitute the primary mechanisms by which the vast majority of neurons die within the cortex *in vivo*. These findings suggest that pharmacologic inhibition of caspase-3 and RIP1K can substantially reduce the level of cellular injury in the most common form of cerebral stroke in humans.

76. Binge Drinking During Adolescence Causes Persistent Behavioral Impairments and Elevated Pro-Inflammatory Proteins in a Rodent Model

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Purpose: Binge drinking among adolescents is an ongoing public health concern. Although binge drinking can also be harmful to adults, the adolescent population is more susceptible to aberrant neurological changes as their brains are still undergoing significant development. The goal of this project is to provide firm evidence that there are changes occurring to physiology in the cerebellum (an area of the brain important for motor coordination and learning) and higher cortical areas after repeated episodes of binge drinking.
Methods: Groups of adolescent (PND 26) and periadolescent (PND 34) rats underwent a series of behavioral tests designed to assess memory, anxiety regulation, and motor function. Subjects were exposed to either ethanol or plain air through a vapour chamber apparatus for five consecutive days (two hours per day). Western blot experiments were conducted using tissue from either the cerebellum or cerebrum to examine the role of NF-kB, PKC-gamma, and caspase-3 (proteins associated with inflammation and cell death) in this model.
Results: Behavioral testing showed significant

differences between the groups up to 60 days after treatment. Both age groups displayed a similar susceptibility to the effects of ethanol exposure. Western blot testing indicated significantly higher levels of the caspase-3 pro-inflammatory protein in the cerebella of ethanol exposed rats, but not in the cortical tissue. NF-kB was found to be elevated in both brain regions.
Conclusion: Behavioral testing shows that there are several potential long-term problems associated with adolescent binge-drinking. Differences on tests related to motor coordination and object memory, which involve the cerebellar and hippocampal brain regions respectively, indicated a persistent impairment. Protein quantification indicated the cerebellum is more susceptible to ethanol-induced inflammation than the cerebrum. These experiments indicate the potential dangers of binge-drinking while the brain is still developing and indicate the need for future studies in this area.

77. Arginine and Glutamate Rich 1 Knockdown is Protective Against High-fat Diet Induced Obesity and Metabolic Dysfunction

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Purpose: ARGLU1, a glucocorticoid receptor (GR) coactivator, was recently found to play an important role in hepatic glucose metabolism. Transcriptome analysis of primary hepatocytes lacking ARGLU1 revealed that in addition to gluconeogenic genes, ARGLU1 also basally regulates a subset of genes involved in lipid homeostasis. To gain insight into whether ARGLU1 is important in lipid metabolism in vivo, we generated liver specific ARGLU1 knockout animals and challenged them with a prolonged high-fat diet feeding.
Methods: Wild-type (WT) and ARGLU1 liver specific knockout (LKO) mice were fed a high-fat diet (HFD) for 14 weeks. Body weight and food intake were monitored weekly. Glucose and insulin tolerance tests were performed after 12 and 13 weeks of diet, respectively. Liver gene expression was analyzed by real time qPCR. In a separate cohort of mice, metabolic cages were used to monitor energy expenditure and locomotor activity.
Results: Remarkably, LKO mice were protected against HFD induced weight gain compared to their WT counterparts, with no difference in food intake. HFD-fed LKO animals had significantly improved glucose and insulin tolerance compared to HFD-fed WT animals. LKO mice also showed increased energy expenditure compared to WT animals. When examining lipid metabolism, we found that HFD-fed LKO mice had significantly lower circulating plasma and liver lipid levels compared to WT HFD-fed animals. QPCR analysis revealed that genes involved in lipogenesis (*Scd1*, *Srebp1c, Fas* and *Acc*) were significantly lower in HFD-fed LKO mice.
Conclusion: Overall, our data show that hepatic ARGLU1 is an important mediator in the development of HFD-induced metabolic dysfunction and represents a potential drug target for the treatment of obesity and non-alcoholic fatty liver disease.

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78. Developing and Evaluating a Patient Decision Aid for Managing Surgical Menopause: The Story Behind the "SheEmpowers" Patient Decision Aid (PDA)

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Purpose: To systematically develop and evaluate an evidence-based patient decision aid (PDA) to help women decide on hormone therapy (HT) to manage symptoms of early surgical menopause and long-term risks.
Methods: The PDA development was guided by the Ottawa decision support framework and involved 3 phases: an exploratory phase to identify women decisional needs; a development phase to identify evidence related to surgical menopause and treatment options and draft an initial prototype; and an evaluation phase to evaluate the prototype and elicit views on acceptability and usability in a non-

clinical setting. For exploratory and evaluation phases, we recruited women from the Edmonton menopause clinics. We searched Medline, TRIP, Dynamed, and others for evidence to inform the content of the PDA. Data on HT outcome probabilities were evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE). All phases were driven by a multidisplinary group of researchers, clinicians and patient partners to ensure women priorities were met.

Results: Informed by identified needs from the exploratory phase an initial prototype of the PDA was drafted and had 4 components: facts about surgical menopause and HT; HT outcome probabilities to develop realistic expectations; a values clarification section to make trade-offs and clarify values associated with HT; and a component on guidance in decision-making. We anticipate including supplemental information on other reasonable treatment options for women consideration. We are currently reviewing the tool with our stakeholders to improve content and presentation and gain perspectives on tailoring to women's needs. The evaluation of the PDA is still pending.

Conclusion: Through our adopted, systematic, evidence-based and multidisciplinary approach we hope to develop a PDA than can empower women with early surgical menopause when making therapy decisions and offer them the information, resources, and skills to effectively manage decision-making about HT and other options.

79. Phytotherapy-induced Hepatocytotoxicity

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Purpose: We report a case of severe-herbal-induced liver injury (HILI) due to Herbalife tea and protein-shake. We aim to show pharmaco-toxicologic and pathology evidence implicating an immune response that produced a cytokine cascade leading to the hypersensitive reaction.

Methods: A 65 year old lady was hospitalized due to hepatocellular injury. Due to the appearance of deep jaundice she was hospitalized. On history ingestion of Herbalife tea and protein-shake was noted.

Results: Liver biopsy revealed necrotizing granulomatous hepatitis, apoptotic cells. PAS diastase stain was showing cluster of foamy macrophages with ceroid pigment, characteristic of toxicity. The severe HILI is consistent with a cholestatic picture.Immunohistochemistry demonstrated bile duct loss. A lymphocyte toxicity assay (LTA) was performed. LTA (% toxicity) was: protein alone 20; tea alone 44; protein+ tea 66.

	Jan	Feb	Mar
AST U/L	1319	606	69
ALT U/L	1096	679	89
GGT U/L	697	899	218
Bilirubin Total mg/dL	3.14	8.0	0.7

The proinflammatory cytokines and chemokine (pg/mL) in serum were elevated as follow: TNF (tumor necrosis factor alpha) 842; IL1 (interleukin) 254; IL6-65; IL13-102; IL8-187. Vascular endothelial growth factor was 5106 pg/mL. Mitochondrial markers M30 and M65 revealed a predominant level of necrosis process versus apoptosis. Discontinuation of the Herbalife products, and treatment with both prednisone and urso-deoxycholic acid resulted in slow resolution of her complaints and in biochemistry (ALT 41 U/L and GGT 49 U/L).

Conclusions: Protein and herbal tea produce mitochondrial toxicity and a strong T-lymphocyte-1 response leading to HILI. This finding is consistent with the reports of combination of protein shake and tea-induced hepatocytotoxicity.

80. Modulation of the Tumor Microenvironment with Manganese Dioxide Nanoparticles to Re-educate Macrophages and Enhance Doxorubicin Efficacy

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Purpose: Hallmarks of tumor microenvironment (TME), including hypoxia, oxidative stress, local acidosis, and tumor-associated macrophages, promotes cancer escape from immune surveillance and resistance to chemotherapy. Recently, our laboratory has developed pharmaceutically acceptable polymer-lipid encapsulated manganese dioxide nanoparticles (MDNPs) which accumulate in tumor tissue and simultaneously modulate multiple factors in the TME by attenuating hypoxia and oxidative stress and neutralizing acidosis. The aim of this study was to investigate the effect of MDNPs on alleviating immunosuppression and enhancing doxorubicin (DOX) efficacy.
Method: The effect of MDNPs on DOX uptake and cytotoxicity in EMT6 murine breast cancer cells were investigated under normoxia or hypoxia. The effect of MDNP on macrophage-mediated cancer cell proliferation was investigated in EMT6 cell and RAW264.7 murine macrophage co-culture. Orthotopic breast tumors were established by injecting EMT6 cells into mammary fat pad of female immunocompetent BALB/c mice. The optimal window of TME modulation by MDNPs to enhance DOX penetration into tumor tissue was determined by treating mice with systemic administration of free DOX 2, 4, or 8 hours following intraveneous injection of MDNPs. To investigate effect of MDNP+DOX therapy on macrophage polarization, tumors were resected on Day 5 and analyzed for cytokine and nitric oxide expression and stained for M1 and M2 macrophage biomarkers.
Results: MDNP treatment enhanced DOX uptake and cytotoxicity in vitro by 190% and 42% respectively compared to DOX alone after 4 h incubation under hypoxia. MDNPs inhibited macrophage-mediated cell proliferation by 23%. At 4 h post-MDNP treatment, DOX accumulation in tumor tissue was the highest, by two-fold, compared to DOX alone. MDNP increased DOX penetration distance by up to 20-fold compared to DOX alone. IHC analysis showed upregulation of M1-related CD86 cells (+51%) and downregulation of M2 marker CD163 (-47%).
Conclusion: This study suggests that MDNP can modulate macrophage polarization and enhance DOX efficacy.

81. Identification and Evaluation of the Prevalence of the Practice of Drugs and Opioids Abuse in Community Pharmacy

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Purpose: Drug addiction is a complex brain illness characterized by obsessive drug craving, often irrepressible, which persists even in the face of exceptionally negative consequences. The drug reliance becomes chronic, with relapses possible even after extended periods of abstinence. Addiction is a significant problem which plagues all members of society including men and women, both young and old.
Method: The study was conducted in various tourist cities of neighboring Himalayan countries. The study data was based on a questionnaire document in which exclusion and inclusion criteria was set. The survey comprised of personal information including: age, gender, status, occupation, and qualifications. Moreover, the questionnaire also gathered additional information about drug use, family, social and financial status, and their views on the effects of drug addiction on society.
Results: The results were analyzed using statistical methods. 94.7% of the participants were between 11 and 20 years old, 55% were unmarried, 57.9% declared their occupation as a student, and 34.2% had qualifications up to primary school. Teenagers are the ones primarily involved in drug obsession. In addition, considering a group of marijuana users, which comprised of 68.4% of the participants, 50% consumed a maximum dose of 1 to 5 grams. 28.9% of this group's use of drugs stemmed from curiosity

and 57.9% of them sourced the drugs from their friends. Furthermore, with regards to the personals views of addict individuals, 36.8% described it as anti-social while 57.9% stated that rehabilitation and treatment should be provisioned for them.
Conclusion: By facilitating good governance and education for teenagers, the imminent issue of drug abuse and addiction can be solved progressively. Moreover, by implementing constructive outcome ventures, we can eradicate the drug craving problem in our society and form healthy nations. However, abstinence is the safest way to live a longer and healthier life.

82. Implementing Pharmacogenomics Testing in Paediatric Care

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Purpose: The Hospital for Sick Children (SickKids) has launched the Clinical Pharmacogenetics Research Pilot study in a collaborative setting, which is available for ambulatory and inpatient consultations within SickKids. The overall goal of the pilot project is to serve as a test-bed to influence the design to plan for a future PGx service, examining the clinical utility and feasibility of implementing such a test into routine paediatric care.
Methods: We have previously demonstrated that genome sequencing technologies show high correlation to targeted PGx testing panels in a paediatric population. Furthermore, as part of the Human Genome Project Canada, a set of 391 variants associated with 14 pharmacogenes with known drug- gene interactions were analyzed.
Results: Most of the children tested had at least one clinically actionable PGx variant, indicating that diagnostic genomic sequencing data can be used for pre-emptive PGx screening. Moreover, each participant in the Human Genome Project carried an average of 4 clinically relevant PGx variants associated with altered metabolism or response to certain drugs.
Conclusion: Based on these results and we initially will utilize a clinically validated targeted PGx testing, but as clinical genome sequencing will be integrated into daily clinical care, we are planning to use this platform as well to generate PGx data for our paediatric patients.

Drug Delivery and Pharmaceutical Technology

83. Are Excipients Inert? Phenytoin: A Follow-up Half a Century Later with New Incompatibility Insights

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Purpose: Excipients are added to aid in the manufacturing process and enhance stability, bioavailability, safety, effectiveness and drug delivery. They are generally considered safe, but they may interact with the API. The 1968 phenytoin intoxication outbreak in Australia, is a classic example of an API–excipient interaction. When administered with $CaSO_4$ the absorption of phenytoin was reduced. When $CaSO_4$ was replaced by lactose, drug absorption was increased, resulting in the observed intoxication. It was hypothesized that phenytoin was converted to a poorly soluble calcium salt. The purpose of this study was to mechanistically investigate the interactions between excipients and phenytoin and to re-examine the hypothesis and interpretation of the previous reports.
Methods: Titration experiments with phenytoin, calcium salts and lactose were performed. NMR was used to characterize the compounds. Isothermal micro calorimetry determined incompatibilities between phenytoin - excipients and phenytoin-milk. Dissolution tests containing $CaSO_4$, lactose or sorbitol as excipients were also performed.
Results: Calorimeter results indicate that phenytoin sodium interacts with $CaSO_4$ in aqueous media forming a compound with low solubility, reducing the amount of dissolved drug available for

absorption. Phenytoin sodium also interacts with lactose through a Maillard reaction that can occur at body temperature. The dissolution profile show a higher release rate from the sorbitol containing compared to calcium or lactose containing formulations. In Canada and the USA, the reference product contains lactose as an excipient, whereas the Canadian generic formulations do not contain lactose.

Conclusion: Phenytoin is commercially available since 1938, much has been learned about API excipient interactions with this drug. After eighty years of clinical use a new incompatibility between phenytoin sodium and lactose was discovered and an incompatibility with calcium was confirmed. This might have important implications for a possible food effect with milk.

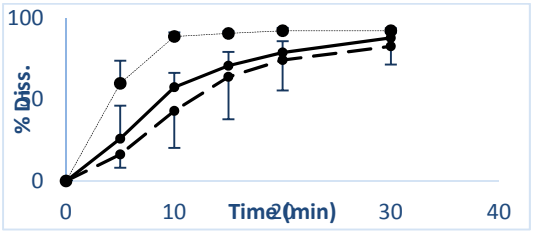

Figure 1. Dissolution profiles obtained for capsules containing phenytoin sodium with lactose (dashed line), phenytoin sodium with $CaSO_4$ (solid line) and phenytoin with sorbitol (dotted line) in water.

84. Transnasal Mucosal Delivery of Brain-Derived Neurotrophic Factor AntagoNATs in Rat Brain using Cationic Liposomal Formulation

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Purpose: Brain-derived neurotropic factor (BDNF) (14 kDa) has important therapeutic implications in chronic neurodegenerative diseases. Delivering biological therapeutics, like BDNF protein across the blood-brain barrier (BBB) is one of the biggest challenges today. The main objective of this study was to develop a trans-nasal mucosal approach for delivering BDNF specific AntagoNAT's (AT's) (oligonucleotides) that inhibit natural antisense transcripts (NAT's) and upregulate endogenous BDNF levels in the brain.

Methods: *In vitro* uptake and transfection studies of Cy5-labeled AT and BDNF AT in saline and cationic liposomes were carried out in RT4-D6P2T rat schwannoma cells. Transfection efficiency was evaluated qualitatively by confocal microscopy and quantitatively by qPCR and ELISA. *In vivo*, transnasal mucosal delivery of AT's was achieved in Sprague Dawley rat model by creating a surgical window in the BBB, which is repaired using nasal mucosal grafts from donor rat. The graft was positioned on the craniotomy creating an internal reservoir directly above the graft. Upon instillation of Cy5-labeled and BDNF AT in saline and cationic liposomal formulations, uptake and BDNF expression levels in different parts of brain were carried out qualitatively by fluorescence microscopy and quantitatively by ELISA.

Results: The *in vitro* and *in vivo* uptake studies using confocal microscopy showed that cationic liposomal formulations resulted in better uptake compared to controls. The *in vitro* transfection in BDNF AT liposomes treated cells resulted in significant increase in BDNF mRNA and protein levels as compared to the controls. The *in vivo* transfection study with BDNF AT in saline and liposomes resulted in four- and five-fold increase in BDNF levels in substantia nigra, respectively, as compared to negative control.

Conclusion: The results show that the novel trans-nasal mucosal delivery and liposomal delivery can help in transporting large molecular weight disease modifying therapies, such as BDNF AT's, in treatment of chronic neurodegenerative diseases.

85. Engineering Functionalized Diamond Nanoparticles for Drug/Gene Delivery: Biodistribution Studies

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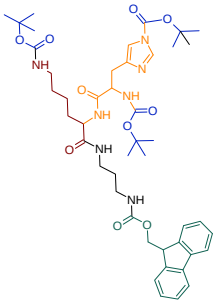
Purpose: To engineer lysine-functionalized nanodiamonds (lysyl-NDs) as biocompatible and efficient gene carriers. Optimization of the design was carried out by grafting histidine as an endosomal membrane destabilizer onto the lysyl-NDs (lysyl-histidyl-ND). However, their specific interactions with the biological system are yet to be

defined. Biodistribution studies will help to elucidate their fate at organ levels and monitor their pharmacokinetics. A suitable chelating agent (defroxamine, DFO) was attached to the functionalized NDs to assist with radio labelling with 89Zr to study the biodistribution in animal models.

Method: ^{1}HNMR was used to confirm synthesis of amino acid conjugates at all steps. The lys-NDs were characterized by size and zeta potential measurements and thermogravimetric analysis. NDs tagged with DFO moieties will be labeled with 89Zr for positron emission tomography in animal models.

Results: Several batches of lys-NDs revealed a surface loading of 1.67 mmoles/gm of ND. The average particle size was 66 nm and zeta potential of +21 mV, showing consistency in all batches and validating the reproducibility of the designed protocol. ^{1}HNMR revealed that the tagged NDs show all DFO protons of the aliphatic chain along with 4 protons of the benzene ring in the aromatic region, confirming the DFO-lysine-linker conjugation. Similarly, lysyl-histidine chemical moiety was synthesized and confirmed using ^{1}HNMR through characteristic peaks at δ 7.34, δ 7.45 (t, 2H, imidazole side chain) as well as presence of 3 Boc protecting groups at δ 1.4 (s 27H).

Conclusion: This study establishes that lysyl- and lysyl-histidine functionalized NDs, as potential carriers for gene therapy, can be labeled with radiotracers for assessment of biodistribution and pharmacokinetic analyses. Understanding the *in vivo* behavior of the functionalized NDs is critical for their translation from benchtop to clinical applications.



Bis boc histidine-mono boc lysine-fmoc diaaminopropane
Chemical Formula: $C_{46}H_{63}N_5O_{10}$
Molecular Weight: 862.02

86. Additive Polyplexes as a Non-viral Delivery System for Combinational siRNA Therapy against CDC20 and Survivin in Breast Cancer and Non-malignant Cells

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Purpose: Conventional breast cancer therapies such as surgery, radiation and chemotherapy have inherent limitations and side effects that warrant a search for alternative therapies, and RNA interference based on small interfering RNA (siRNA) seems to be a promising approach. We have developed a library of cationic polymers based on 1.2 kDa polyethylenimine (PEI) to transport siRNA safely. In this study, we introduced additive polymers such as hyaluronic acid (HA), polyacrylic acid (PA), dextran sulfate (DS) and methyl cellulose (MC) while making siRNA/PEI complexes to increase the efficacy of siRNA.

Methods and Results: We prepared additive polyplexes by first mixing siRNA and additive polymers followed by addition of PEI substituted with linoleic acid (PEI-LA). The physicochemical characteristics of these polyplexes suggested similar size among different additive polymers, while zeta potential has decreased drastically with negatively-charged additive polymers. A faster dissociation of complexes was evident with negatively-charged additive polymers. The uptake of complexes determined by flow cytometry and confocal microscopy suggested higher uptake of siRNA with additive polyplexes compared to regular siRNA/PEI complexes. Combinational siRNAs against CDC20 and survivin were delivered in breast cancer cells, MDA-MB-231, SUM149PT, MDA-MB-436 and MCF7, and additive polyplexes with HA and PA were the most successful complexes with >40% of cell growth inhibition. The cell growth of non-malignant cells, MCF10A and HUVEC were inhibited to some extent, while hBMSC and HEK293T were the least affected by the combinational siRNA therapy.

Conclusions: A better dissociation of polyplexes with negatively-charged additive polymers, HA, PA and DS resulted into higher cell growth inhibition

compared to without or neutral (MC) additive polymer. Even though the combinational siRNA therapy showed improved therapeutic efficacy in breast cancer cells, the side effects on nonmalignant cells were evident as well, and more selective targets might be needed to minimize the side effects.

87. Nano-sized Droplets of Self-Emulsifying System for Enhancing Oral Bioavailability of Etoposide in Rats

Nayab Khalid[1,2], Muhammad Sarfraz[3,4], Mosab Arafat[3], Muhammad Akhtar[2], Nisar-Ur-Rahman[1,2], Raimar Löbenberg[4].
[1]Department of Pharmacy, COMSATS Institute of Information Technology, Abbottabad, Pakistan; [2]Faculty of Pharmacy and Alternative Medicine, The Islamia University of Bahawalpur, Pakistan; [3]College of Pharmacy, Al Ain University of Science and Technology, Al Ain, UAE; [4]Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, Canada.

Purpose: This study was carried on to investigate the ability of self- nano-emulsifying system to enhance the oral bioavailability of Etoposide.
Method: A series of self-emulsifying system formulations with etoposide were prepared consisting of medium chain triglycerides, Polysorbate 80, diethylene glycol mono-ethyl ether and propylene glycol monolaurate. Test formulation was characterized in terms of globule size, zeta potential, PDI, TEM images and in vitro drug release profile was evaluated in comparison with a drug suspension and the commercial product VePesid® in simulated intestinal fluid medium, pH 6.8. The PK parameters and oral bioavailability of etoposide suspension and etoposide in the self-nano-emulsifying system was assessed and compared with the commercial product (VePesid® capsule) using 30 Male Sprague–Dawley rats. Blood samples were collected for up to 24 h, and VP-16 analyzed using a validated HPLC assay.
Results: Pharmacokinetics data showed that the mean values for AUC of etoposide in nano-sized droplets of the self-emulsifying system was found to be 6.4 folds higher than drug suspension and 2.4-folds higher compared to the commercial products VePesid® capsule. Similarly, the mean values for C_{max} of etoposide in nano-sized droplets of self-emulsifying system was found to be higher (1.13± 0.07 µg/ml µg.h/ml) compared to the VePesid® capsule (0.62± 0.09 µg/ml) and drug suspension (0.13± 0.07 µg/ml).
Conclusion: The nano-sized droplets of the self-emulsifying system was found to be able to increase the oral bioavailability of the BCS Class IV chemotherapeutic agent etoposide up to 10.4-fold by enhancing the dissolution and absorption of the drug.

88. Microwave Enhanced Protein Folding

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[1]Institut National de la recherche scientifique-Énergie Matériaux et Télécommunications

Purpose: The refolding process is a competing reaction with misfolding and aggregation events. It's guided by reversible electrostatic interaction and exchangeable disulfide bonds. Once protein folding is initiated from its unfolded state, it is a very rapid process and can get stuck along the way into kinetic traps. In these traps, molecular dynamics are too slow or movement is blocked by entanglements, preventing further evolution to the thermodynamically most stable structure. In this work we examined whether microwave irradiation can replace the need for chaperones promoting the reversibility of electrostatic interactions and also accelerate the disulfide isomerization process.
Method: Ribonuclease A (RNase A) was chosen as a model due to its peculiar catalytic activity that can be exclusively observed if the folding is successfully achieved, which allows monitoring of the kinetics of refolding. We started by optimizing the enzymatic assay of the native RNase A, then a first screen was done by exposing the RNase A to a microwave with an integrated cooling system for 30 min at different power while the temperature was kept constant. Successively, solutions of misfolded enzyme will be exposed to different power levels and temperatures to determine whether folding can be, at least partially, reactivated due to stimulated molecular dynamics.
Results: The catalytic activity of the ribonuclease A was not affected by microwave exposure. Our hypothesis is that the simultaneous cooling was responsible for avoiding damage to the enzyme. The targeted result is to establish microwave irradiation and additive conditions to achieve high conversion to the desired folded structure while maintaining the biological activity of the enzyme.
Conclusion: The microwave irradiation at fixed

temperature exhibited promising results as a new tool for enhancing the refolding process without the need of chaperones.
Acknowledgments: This study is supported by the Natural Science and Engineering Council of Canada (RGPIN-2015-04254)

89. Phenylbutyrate Loaded Solid Lipid Nanoparticles could Improve Cognition in Alzheimer's Disease Induced Animal Model

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Purpose: Phenylbutyrate, a histone deacetylase inhibitor, considered to be effective in halting the progression of Alzheimer's disease by reducing hyperphosphorylation of tau protein, preserving neuronal cell density and preventing the formation of intraneuronal A□. To act efficiently, considerably large dose of phenylbutyrate should be administrated. Designing a sustained delivery system is a promising way to reduce the administration times. Considering the characteristics of various delivery systems, solid lipid nanoparticles (SLNs) were seemed suitable for such purpose. This study aimed to evaluate the biodistribution and effectiveness of the phenylbutyrate loaded functionalized SLNs.
Method: Herein the phenylbutyrate loaded SLNs were prepared and functionalized with polysorbate80 (S80) or phosphatidylserine (PS) for proper brain delivery. The effect of these delivery systems on memory-related behavioral of Alzheimer induced animals (intracerebroventricular streptozotocin injected model) were studied using Morris water maze test. Their biodistribution in brain were evaluated by DiR-fluorescent marker. The hippocampal neurons were counted using the Cresyl violet staining.
Results: The particle sizes of 154, 179 and 161nm were acquired for non-functionalized, S80-functionalized and PS-functionalized SLNs, respectively. The significant improvement of memory-related behavioral had observed in animals treated with functionalized SLN comparing to other groups. Their higher brain concentration, in comparison to the non-functionalized SLNs, suggested the efficacy of functionalization. In histopathological studies, the functionalized SLNs treated groups have significantly higher neuronal count than the control group.
Conclusion: The acquired results suggested the suitability of formulations for brain delivery of their laden drug, their potential in improving the cognition and preserving the hippocampus' neurons of experimented animals. On the other hand, the functionalized SLNs could reduce the required administration times and doses.

90. Precise Orientation of Thermally-sensitive Biomolecules using DNA Nanostructures: An Exploration of Non-thermal Techniques for Controlling DNA Nanoassemblies

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Purpose: The commercialization of synthetic DNA strands has led to exquisite control over sequence design. With the predictability of the A-T, C-G DNA alphabet, many researchers have begun to design DNA nanostructures to precisely position functional groups in 2D and 3D environments. This approach has been successful in positioning small molecules, fluorophores, polymers, etc. However, many opportunities remain in the field of biomolecules, where enzymes, antibodies, and proteins could be arranged to create novel classes of drugs. To date, such biomolecule-DNA nanoassemblies have been limited due to the high heat required to assemble DNA structures. Here, we pursue the use of non-ionizing radiation to control DNA assembly at room temperature.
Method: Two sources of non-ionization radiation were used: a THz pulse and a cooled microwave reactor. Three different DNA nanostructures were screened for both assembly and disassembly. A variety of biomolecules (enzymes, antibodies, etc) were exposed to identical assembly/disassembly conditions, and their activity evaluated following exposure. As a final test, a biomolecule was conjugated to one of the DNA strands required for the nanostructure, and structure assembly and activity was evaluated.

Results: Room-temperature microwave anneal was found to produce the desired thermodynamic structure with 82±8% yield (compared to ~30% yield when no anneal was used). Exposure to THz rapidly disassembled structures. Of the six biomolecules tested, 5 retained 100% activity following the microwave assembly. The sixth saw a 25% reduction in activity. Assembly of a nanostructure using a thermally-sensitive biomolecule-DNA conjugate was successful.
Conclusion: We were able to both assemble and disassemble DNA nanostructures using novel, biomolecule-friendly techniques. More importantly, we were able to assembly a biomolecule-labeled nanostructure without denaturing the biomolecule – something that would not be possible using traditional thermal assembly.

91. Biomimetic Vector (BMV™): An Innovative Skin Delivery System

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Purpose: BMV™ is a proprietary delivery microsystem developed and patented by Biomod. It is composed of biomimetic ingredients and allows the incorporation, the protection and the transport of actives through the *stratum corneum* and deeper layers of the skin. The goal is to demonstrate that BMV™ improve the skin delivery of actives.
Methods: BMV™ microparticles were characterized: the size and the morphology were visualized by optical microscopy, encapsulation of actives was demonstrated by laser scanning confocal microscopy, and active content was measured by HPLC-UV. Caffeine was used as a model molecule to study skin delivery. *In vitro* permeability assays on Franz cells with Strat-M® membranes were conducted to compare the diffusion of caffeine in solution (n=6) and loaded in the BMV™ technology (n=3). Wash out of the donor compartments was performed at 8 hours to evaluate the reservoir effect of the microsystem. A comparable permeability study was performed on human skin biopsies assembly on Franz cells.
Results: The caffeine-loaded microparticles size ranged from 2-15 µm and are spherical. Coumarin-6 (lipophilic) and Rhodamine-B (hydrophilic) were successfully loaded in the microparticles demonstrating the potential of the BMV™ to incorporate a large variety of molecules. Diffusion in the donor compartments of caffeine through the Strat-M® was 1,7 times faster and 3 times higher for the BMV™ system than the caffeine in solution. After the wash out, 35% of the total diffused dose was recovered in the acceptor compartments between 8 and 24 hours suggesting a reservoir effect. The same diffusion rate and tank effect was observed on human skin biopsies.
Conclusion: Strat-M® can be used as a non-animal model to predict the permeability of BMV™. Microparticles can be used to improve the skin diffusion of molecules and promote a reservoir effect. Further studies with different molecules and formulations are ongoing.

92. Photocleavable Hydrogel-Coated Upconverting Nanoparticles for On-Demand Drug Delivery of Ultra-small Gold-Doxorubicin Conjugates

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Purpose: Light-triggered drug delivery offers precise control of the dosage, timing and location of drug release in a non-invasive manner. However, the typical wavelengths used for photoreactions are in the ultraviolet (UV) or visible (Vis) range and have limited penetration in biological tissues. Near-infrared light (NIR) can penetrate deep into living tissues, has a low autofluorescence background and is non phototoxic. Lanthanide-based upconversion nanoparticles (UCNPs) can absorb NIR light and re-emit the UV-vis light required for the photoreactions to trigger drug release. Furthermore, ultra-small gold-doxorubicin (Dox) conjugates have higher cytotoxicity to apoptosis-resistant melanoma cells than Dox alone. This research develops a photocleavable hydrogel coating on UCNPs for on-demand delivery of such conjugates upon NIR radiation.
Methods: LiYF4:Tm,Yb UCNPs were synthesized and coated with a hydrogel of nitrobenzyl photocleavable crosslinks. Doxorubicin was conjugated to gold nanoparticles and loaded into the hydrogel. Its release was measured during either on (1 min) or off (50 min) states of an NIR laser at 1.8 W/cm2. Drug release curves were then quantified.
Results: As expected, the gold-Dox conjugates were

released from the photocleavable hydrogel upon NIR radiation. The rate of drug release can be tuned via laser power and irradiation time.
Conclusions: Chemotherapeutic drugs can be released on-demand via NIR radiation from photocleavable hydrogel-coated UCNPs, thus offering greater control over dosage, timing and location of chemotherapy drug release at tumor site.

93. Hyperthermia-mediated Drug Delivery Increases Cisplatin Sensitivity and Accumulation Resulting in Improved Efficacy in Triple Negative Breast Cancer

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Purpose: Triple-negative breast cancer accounts for more 15% of breast cancer diagnoses and an even higher percentage of breast cancer-related morbidity. However, triple-negative breast cancer patients do not benefit from recently developed targeted therapies and therefore novel treatments must be sought. Hyperthermia has shown promise in sensitizing breast cancers to chemotherapy and improving patient outcomes. The main goal of this work is to assess the efficacy of hyperthermia-triggered release of cisplatin from thermosensitive liposomes and to relate the *in vivo* efficacy to *in vitro* measures of toxicity.
Methods: The *in vitro* sensitivity to hyperthermia, cisplatin, and the combination of the two interventions was measured using monolayer cell viability assay, clonogenic assay, and multicellular tumour spheroid assay. *In vitro* molecular biological response to hyperthermia was determined by measuring heat shock protein mRNA expression using quantitative PCR and expression of BRCA1, an important DNA damage repair protein, by western blot analysis. *In vivo* biological response to hyperthermia was measured by immunohistochemical staining of heat shock proteins. Tumour accumulation of cisplatin was also measured. The efficacy of thermosensitive cisplatin liposomes, non-thermosensitive cisplatin liposomes, or free cisplatin alone or in combination with hyperthermia was assessed in two orthotopic models of triple-negative breast cancer.
Results: Hyperthermia-triggered drug delivery significantly increased drug concentrations within the tumor, while hyperthermia degraded BRCA1 and increased CDDP sensitivity of breast cancer cells. In both tumour models, thermosensitive cisplatin liposomes in combination with hyperthermia provided the longest median survival times.
Conclusion: Cisplatin-containing thermosensitive liposomes provided the longest median survival times in mice bearing tumors sensitive to cisplatin. However, it was in mice with tumors less sensitive to cisplatin that the combined effects of increased tumor accumulation of cisplatin and impaired DNA damage repair mechanisms resulted in the greatest increase in median survival for thermosensitive cisplatin liposome treatment compared to cisplatin alone.

94. Liposomal Delivery of a Doxorubicin and Niraparib combination for the treatment of High Grade Serous Ovarian Cancer

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Purpose: Results from clinical trials investigating the safety and efficacy of PARP inhibitors (PARPi) in combination with PEGylated liposomal doxorubicin (PLD) for the treatment of ovarian cancer (OC) have yielded promising results. Consequently, the aim of this study was to investigate the synergistic potential between niraparib (NIR) and doxorubicin (DOX) at specific molar ratios. Following this, we aimed to formulate these drugs into a liposomal nanoparticle.
Methods: A panel of five OC cell lines were selected to assess the effect of the DOX:NIR combination. IC_{50} values were obtained for 11 DOX:NIR molar ratios and used to calculate the combination index (CI) values as described by Chou and Talalay. NIR liposomes were synthesized via ethanol emulsion followed by extrusion. Particle size was measured using DLS and loading was determined using HPLC. *In vitro* release studies were performed under sink conditions with 50mg/mL BSA.

Results: DOX:NIR was found to be synergistic at ratios of excess NIR and antagonistic at ratios of excess DOX across all 5 cell lines. NIR-loaded liposomes were 131.9 ± 31.24 nm in size, with the average concentration of encapsulated NIR being 2.39mg/mL. Release of NIR was sustained over a 5-day period, with approximately 25% of drug released.
Conclusion: The results of this study have shown that DOX:NIR are synergistic at ratios where NIR is in excess. We hypothesize that this effect will also be seen *in vivo* if DOX:NIR are delivered to the tumor site at a synergistic ratio. As demonstrated with the recent approval of Vyxeos™, nanoparticles can deliver synergistic drug combinations to the tumor site to yield a superior *in vivo* response. The next steps of this study is to formulate a dual-encapsulated liposome of DOX:NIR at a fixed synergistic ratio and to assess efficacy in a relevant bioluminescent model of HGSOC.

95. Stimuli-sensitive Theranostic Nanoparticles for Targeted Imaging-Guided Drug Delivery

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Purpose: The existing delivery systems for insulin all suffer from inability to regulate insulin without patient intervention. Targeted drug carriers using polymeric nanoparticles holds particular promise to enhance the delivery of immunoregulatory agents to treat type 1 diabetes (T1D). The aim of this study was to synthesize and characterize stimuli-responsive, thermosensitive, immunoregulatory-bearing carriers for potential use in image-guided targeted delivery and on site controlled release of nanocongugates.
Methods: Hyperthermia magnetic nanoparticles (HMNs) made out of Gd-Zn-Fe were synthesized with self-controlled Curie temperature (Tc) in the range of 39-40^{o}C, using co-precipitation method. The characterization data of the Gd-substituted Zn Ferrite particles with that of the Zn Ferrite particles were compared. Transmission electron microscopy (TEM) of Gd-Zn-Fe nanoparticles was evaluated. The magnetic resonance imaging (MRI) relaxivities of the HMNs were measured in the temperature range 25-45^{o}C.
Results: Addition of Gd in small amounts led to modulate Tc linearly with the amount of Gd-substituted Zn Ferrite particles. TEM micrograph of Gd-Zn-Fe nanoparticles showed a dispersion of spherical particles with a narrow size distribution, with mean diameter of 5.5 ± 0.9 nm. The nanoparticles systems developed generated sufficient heat and stopped heating at the measured Tc, which is modulated by the fraction of the composition. The measured R1 and R2 values at different concentrations showed linear increase of the relaxation rate. The increase of r2 with temperature was relatively large and linear; while the increase in r1 was small and exhibits poor linearity.
Conclusion: The synthesized HMNs have the intrinsic ability to self-regulate their heating level to the desired therapeutic range. The temperature of HMN that have Tc in the therapeutic range will rise only up to the Tc when the particles are subjected to an oscillating magnetic field, and further increasing the intensity of the field will not increase heating beyond their Tc.

96. Optimization of a New pH-Responsive Pore Former for Controlled Release Coating

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Purpose: Many drugs exhibit pH-dependent solubility and varying absorption along the GI tract, which may result in unexpected toxicity and reduced efficacy. One approach to ameliorate this problem is to utilize pH-responsive permeability modifiers (i.e. pore formers) to compensate changes in drug solubility. Previously, we demonstrated that pH-sensitive nanoparticles in ethylcellulose film could provide pH-responsive drug release while mitigating major drawbacks of conventional pore formers, including high viscosity of the coating suspension and leaching from the coating. In this work, we aim to optimize the composition of the nanoparticles to maximize the pH-responsiveness and mechanical strength while minimizing the leaching.
Methods: The nanoparticles were synthesized by a one-pot polymerization method with various molar ratios of polysorbate 80 (PS80) and polymethacrylic acid (PMAA) grafted onto starch and cross-linking agent (MBA). A central composite design (CCD) was used to optimize the MAA, MBA, and PS80 ratios in the feed. The experiments were performed

based on a full 2^3 factorial design with six center point replicates and six axial points. The effects of pH-responsive permeability, tensile strength, and leaching of the composite membranes were evaluated using side-bi-side diffusion cells, tensile testing, and weight loss study, respectively. Statistical analysis were conducted using JMP10 software.

Results: A response surface was constructed using a CCD which the optimal composition was found and verified with further experiments. From the analysis, the pH-responsiveness was found to be dependent on MAA and MBA ratio, tensile strength was dependent on MBA and its interaction with PS80, and weight loss was dependent on MBA only.

Conclusion: Significant factors of each response were found, and the optimized composite membrane showed the most desirable pH-responsiveness and tensile strength with minimum leaching. The influence of the optimized nanoparticle pore former on pH-dependent drug release profile will be further investigated using spray-coated bead formulation.

97. Microemulsion-based System for Transdermal Drug Delivery of Methimazole in Cats

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Purpose: Hyperthyroidism is one of the most common feline endocrine disorders due to excess production of active thyroid hormone in middle-aged cats. The management involves oral or transdermal antithyroid drug delivery. The use of transdermal medications in cats has become popular in veterinary medicine due to the ease of administration compared to oral medications. Our hypothesis is that microemulsion-based system can improve the in vitro flux of Methimazole using a Franz cell model.

Method: Different concentrations of 0.25%, 0.5%, and 1% of Methimazole were incorporated into Labrafac-based microemulsion formulations with Labrasol as surfactant and Plurol Oleique as cosurfactant to be used for transdermal delivery of Methimazole. The in vitro studies were carried out using Franz cell apparatus with a diffusional surface area of 1.79 cm^2 and synthetic membranes. Purified water was used as the receptor fluid and the temperature maintained at 32 ± 0.5°C. The withdrawn samples were appropriately diluted and calculated at different time points 30 min, 1, 2, 4, and 6hrs using HPLC.

Result: The preliminary result of in vitro study indicated that the foamable microemulsion system might be a candidate carrier for transdermal delivery of Methimazole. Percentage release through hydrophobic synthetic membranes into the receptor media were found to be 56.2%, 68.1%, 72.6% for the following concentrations 0.25%, 0.5%, 1% respectively.

Conclusion: The microemulsion system appears to be one of the promising tools for percutaneous delivery of Methimazole. The release profiles obtained from in vitro permeability tests might be used for predicting the in vivo permeability of the formulation. Findings from the current research work suggested that the developed Methimazole loaded ME-based system might be potential vehicle for enhancing the topical penetration of Methimazole.

98. Affinity Based Release of Protein Therapeutics to Treat Retinitis Pigmentosa

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Purpose: Retinitis pigmentosa (RP) is a genetic disease that causes rod photoreceptor degeneration, subsequently leading to the loss of cone photoreceptor cells, causing blindness. Ciliary neurotrophic factor (CNTF) and rod-derived cone viability factor (RdCVF) have the potential to treat patients affected by RP. However, topical applications and bolus injections of therapeutics may be limited by drug clearance and overdose, respectively. To mitigate these risks, we developed an affinity-based system for sustained protein delivery. Specifically, an injectable physical blend of hyaluronan and methylcellulose was modified with a

peptide binding partner of the Src homology 3 (SH3) domain allowing the controlled release of SH3-containing fusion proteins.
Methods: The SH3 binding peptide was immobilized onto thiol-modified methylcellulose. The SH3-CNTF and SH3-RdCVF fusion proteins were separately purified from *E. coli*. Using ELISA, the release of SH3-CNTF was investigated *in vitro*. A TF1-α cell proliferation assay was performed to evaluate bioactivity SH3-CNTF. Finally, both *in vivo* bioactivity and controlled release of SH3-CNTF were evaluated in wildtype mice.
Results: Purified CNTF-SH3 and RdCVF-SH3 were verified using mass spectrometry. Maleimide-functionalized SH3-binding peptides were grafted onto the gel, and *in vitro* investigations demonstrated sustained SH3-CNTF release over 10 days. Furthermore, released samples maintained bioactivity (≥ 75%) *in vitro*. *In vivo*, the intravitreal sustained delivery of SH3-CNTF showed the expected downregulation of visual cycle genes, demonstrating effective release and bioactivity. Finally, morphology of the retina after 7 days confirmed the bioinertness of the vehicle.
Conclusions: Our affinity-based system constitutes a new intraocular delivery platform for the treatment of retinal degenerative diseases, and has prompted us to apply this strategy to other therapeutics in the future.
Acknowledgments: We are grateful to the Canada First Research Excellence Fund of Medicine by Design (to VW and MSS) and the NSERC CREATE in M3 (to CT) for funding.

Pharmaceutical and Analytical Chemistry

99. Investigating the Correlation between Miscibility and Physical Stability of Solid Phospholipid Dispersions Using Fluorescence-Based Techniques

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Purpose: Amorphous solid phospholipid dispersion (SPD) has been widely used to enhance the bioavailability of water-insoluble drugs, since amorphous drug shows faster dissolution than its crystalline counterpart due to higher free energy. However, amorphous drugs tend to recrystallize in SPD with time, negating the desired enhancement on dissolution. It is also challenging to evaluate drug-phospholipid miscibility although various techniques have been used for this purpose. Therefore, the objective of this study was to investigate the feasibility of using fluorescence-based techniques to assess the drug-phospholipid miscibility, and to probe the correlation between miscibility and physical stability.
Methods: Autofluorescent indomethacin-phospholipid (IDM-PL) thin films were prepared by drop casting method. The miscibility was characterized by infrared (IR) spectroscopy, fluorescence spectroscopy and fluorescence microscopy. The physical stability of IDM-PL stored at 40℃ was evaluated by fluorescence imaging and correlated with the initial state of IDM-PL as revealed by different spectra.
Results: Doublet emission peaks were observed in the fluorescence spectra of high drug-loading samples, suggesting the existence of two local polarity environments. Amorphous-amorphous separation and amorphous-crystalline transformation with storage time were visualized by fluorescence imaging using a monotonic method. The experimentally determined drug loading limit of IDM-PL system was 30%, above which amorphous-amorphous separation was thermodynamically favored, leading to the recrystallization of IDM in the drug-rich phase due to the loss of crystal inhibition effect rendered by phospholipid. The results showed good correspondence to IR, and further confirmed the phase transformation suggested by such conventional techniques.
Conclusion: Fluorescence techniques were successfully used to evaluate drug-phospholipid miscibility for the first time. The miscibility and physical stability of IDM-PL system were determined, visualized and correlated in this study. Fluorescence techniques show promise in evaluating the interactions between autofluorescent drugs and phospholipids, aiming to build robust SPDs that are resistant to recrystallization during storage.

100. Use of Confocal Fluorescence Imaging Techniques to Understand Phase Separation Behaviour during Dissolution of Amorphous Solid Dispersions

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Purpose: For amorphous solid dispersions (ASDs) to be effective, it should be stable not only during storage but also during dissolution. Ideally, one would want to maintain its high energy state in order to generate supersaturation during dissolution. Unfortunately, when highly water soluble polymers are used as carriers for the formulation of ASDs, significant moisture absorption leads to moisture induced phase separation. The aim of this study is to understand moisture induced phase separation for different drug loadings through confocal fluorescence imaging.
Method: Moisture induced phase behavior was studied using ASD systems: indomethacin-PVP (IND-PVP) and ritonavir-PVP (RTV-PVP). Small amount of Nile red dye was incorporated to stain the hydrophobic domain. Solid dispersions of different drug loadings were prepared by solution casting method. After drying, the ASD was exposed to water and then phase separation behavior was probed by confocal fluorescence imaging.
Results: Clear phase separation was not visible through fluorescence imaging in IND-PVP samples, possibly because the domain size of IND-PVP is smaller than the resolution of the confocal microscope. In the case of RTV-PVP samples, as drug loading was increased from 10% to 50%, phase separation domain size also increased.
Conclusion: Confocal fluorescence can be used to monitor moisture induced phase separation in ASDs. Higher drug loading led to larger domain sizes and such difference in phase behavior between different drug loadings may help explain the difference in release rate.

101. Investigation into the Factors Associated with Anesthetic Failure of Hyperbaric Bupivacaine, including the Potential Role of Cold Exposure on Bupivacaine Degradation

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Purpose Hyperbaric bupivacaine (0.75% in dextrose) is commonly used for spinal anesthesia in obstetrics. Occasional clusters of anesthetic failures occur in this setting, not readily attributable to clinical factors. We hypothesized that exposure to cold temperatures is related to bupivacaine instability.
Methods An electronic survey was distributed to Canadian anesthesiologists regarding spinal anesthesia practice, and to invite submission of failed bupivacaine samples for analysis. A separate survey for hospital pharmacists focused on bupivacaine logistics. UV spectrometry, differential scanning calorimetry and HPLC were used to evaluate temperature effects on bupivacaine stability. Mass spectrometry (MS) was used to observe bupivacaine degradation. Secondary MS/MS analysis evaluated those peaks identified as being most common in the failed or temperature-altered samples.
Results Canadian obstetric anesthesiologists report similar practice and mainly use hyperbaric bupivacaine for spinal anesthesia. Pharmacists surveyed indicated facility storage at room temperature but variability during shipping. No standard procedure for failure reporting was identified. Analysis of bupivacaine showed a slight decrease in bupivacaine concentration or UV spectral changes when samples were incubated at temperatures $\leq$ 4°C. Mass spectrometric analysis was complex, with inconsistent ion formation for samples representing clinical failures that were different than the ions observed for cooled vs uncooled bupivacaine solutions. However, temperature-related changes were noted for dextrose in which dextrose-related ions were formed.
Conclusions Canadian clinical practice and product handling of hyperbaric bupivacaine is fairly consistent. The effects of cold exposure and clinical

handling produce a complex and possibly inconsistent reaction that will require further analysis on a larger sample size to elucidate the mechanisms. Most respondents indicated they are interested in a formal reporting and collection process to better understand this issue.

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102. Developing an Assay to Quantify Nuclear Receptors by Mass Spectrometry

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Purpose: Nuclear Receptors (NR) are a family of 48 (49 in mice) ligand activated transcription factors that control the expression of genes involved in a wide range of physiological processes and form one of the largest classes of drug targets. To date, there has not been any method to quantitatively compare protein levels between different NRs. Our goal is to generate a tissue-wide, quantitative NR *protein expression* profile using targeted proteomics.
Methods: A workflow was developed to tryptically digest all the NRs *in silico* and filter peptides for uniqueness, optimal length (6 – 20 AA long), and absence of post-translational modifications. Using the Global Proteome Machine (GPM) peptide database, 8 peptides for each protein were chosen to validate on a QExactive HF mass spectrometer. Validation was done by comparing HEK293 cells transfected to overexpress a NR to a control. Proteins were digested with Trypsin and Lys-C using the FASP protocol. Tissues were isolated from C57Bl/6 mice, homogenized and digested.
Results: For the 49 NRs, our workflow identified 826 unique peptides meeting our criteria. 306 of the 826 candidate peptides were found in the GPM database, with 45 of the 49 receptors represented. We have acquired NR expression plasmids and overexpressed them in HEK293 cells. Using this HEK293 system, peptides have been selected and validated for 25 of the receptors to date. The protein expression profile of GR was performed across 9 different tissues (adrenal gland, liver, lung, spleen, brain stem, cerebellum, cerebrum, hypothalamus, and spinal cord). Among these tissues, GR expression was the highest in liver, spleen, lung, and cerebrum. Heavy labeled peptides have been purchased for the NRs whose peptides have been validated in the method above.
Conclusion: This assay will quantitate low abundance NR proteins which are highly relevant drug targets normally missed by untargeted proteomics.

Pharmacokinetics and Pharmacodynamics

103. *In silico, in vitro* and *in vivo* Pharmaceutical Investigations of a Novel Skeletal Muscle Regenerator

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Purpose: A novel skeletal muscle-regenerating compound MyoNovin was developed through synthesis of two nitro groups onto guaifenesin to deliver nitric oxide to skeletal muscle with a potential to treat muscle atrophy. The purpose of this study was to examine MyoNovin's pharmacological effects and delineate for the first time an analytical assay to characterize pharmacokinetics and its single dose tolerability.
Methods: *In vitro* cardiotoxicity was assessed using

human cardiomyocytes (RL-14) while effects on CYP3A4 metabolic enzyme and antioxidant activity were examined using commercial kits. A novel HPLC assay was developed to measure MyoNovin concentration in serum, and delineate initial pharmacokinetic and acute cardiac and renal toxicity after intravenous administration (20 mg/kg) to male Sprague-Dawley rats. *In silico* software packages were used to predict the physicochemical and biopharmaceutical properties.

Results: An HPLC assay was successfully developed. MyoNovin was determined to have a short serum half-life ($t_{1/2}$) of 0.16 h, and a volume of distribution V_{ss} of 0.62 L/kg. Biomarkers of MyoNovin cardiac and renal toxicity did not differ significantly from baseline control levels. *In vitro,* MyoNovin was not cytotoxic to cardiomyocytes at concentrations below 8 μM and did not inhibit CYP3A4 or show antioxidant activity. MyoNovin showed relatively high lipophilicity with a LogP value of 3.49, a 20-fold higher skin permeability (19.89 cm/s*10^7) compared to guaifenesin (0.66 cm/s*10^7), and ~10-fold higher effective jejunal permeability (2.24 cm/s*10^4) compared to guaifenesin (0.26 cm/s*10^4).

Conclusions: Pharmacokinetics following IV administration of MyoNovin were delineated for the first time in a rat model. Preliminary single 20 mg/kg dose assessment of MyoNovin suggest no influence on serum cardiac troponin or urine β-N-Acetylglucosaminidase. The predicted high lipophilicity and skin permeability of MyoNovin render it a potential candidate for transdermal administration while its favourable intestinal permeation suggests it may be suitable for oral administration.

104. A Physiologically-based Approach to the Pharmacokinetics of Anti-TNF Agents in Pediatrics

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Purpose: Monoclonal antibodies (mAbs) targeted against tumour necrosis factor (TNF) are used in children as young as two years old for treatment of autoimmune diseases. Little is known about how growth and maturation may impact the pharmacokinetics (PK) of these agents. With the same weight-based dose, young children (2-6 years) typically achieve lower exposures when compared to adults, while adolescents (12-18 years) do not. This work explores the effects of growth and maturation on the PK of anti-TNF mAbs using a physiologically-based pharmacokinetic (PBPK) modelling approach.

Methods: A PBPK model was developed in PK-Sim and Mobi (open-systems-pharmacology.com) to describe the subcutaneous absorption, distribution and elimination of anti-TNF mAbs in adults. The physiological parameters in the adult model were then adapted to create a pediatric model with anatomy and physiology according to known values in literature. Following evaluation of the pediatric model using observed pediatric PK data, sensitivity analyses were performed to identify the key physiological parameters in the pediatric model that were most influential for predicting exposure differences between adults and children.

Results: The adult and pediatric PBPK models for adalimumab, infliximab and golimumab adequately predicted the observed PK data and associated inter-individual variability. Based on the sensitivity analysis, the fast rate of subcutaneous absorption in children was driven by a fast lymph flow rate. Differences in distribution were related to differences in capillary surface area and leaky: tight tissue mass ratios. Low concentrations of the neonatal Fc receptor (FcRn) in the vascular endothelium of young children may be responsible for the PK differences in elimination.

Conclusions: A PBPK modelling approach to pediatric PK prediction for anti-TNF mAbs was demonstrated. Further research will be concerned with extrapolating the PBPK model to infants.

105. Correlating Protein Expression of Human Hepatic Uridine Diphosphate Glucuronosyltransferases (UGTs): Implications for UGT Protein Co-regulation

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Purpose: Uridine diphosphate glucuronosyl-transferases (UGTs) are Phase II conjugation enzymes involved in the metabolism of numerous drugs, nutrients and environmental chemicals. Accumulating evidence suggests that different UGT

isoforms can physically associate with each other to increase activity and clearance capacity.
Methods: A protein expression data set containing UGT1A1, 1A3, 1A4, 1A6, 1A9, 2B7, 3A1, and 3A2 was generated using the same western blot protocol, and sampling a liver archive multiple times. We compared total abundance of UGT proteins and correlation between pairs of isoforms. Age, body mass index, ethnicity and sex were investigated as co-variables. Analysis was performed in GraphPad Prism 6 (La Jolla, CA).
Results: The most abundant isoforms in human liver are UGT1A4 and UGT2B7, except in age >65 where UGT3A1 and 3A2 are upregulated. Protein abundance and associations did not differ with sex, ethnicity or BMI. UGT1A1/1A6 and UGT1A6/1A9 always correlate with excellent correlation coefficients, regardless of age ($p<0.0001$ both, $r=0.97$ and 0.82, respectively). The UGT1A3 isoform was only analyzed in adults and highly correlates with UGT1A1, 1A4, 1A6 and 1A9 ($r>0.85$, except 1A4 $r=0.62$, and $p<0.0001$ for all). Some isoforms only correlate significantly in adolescence or adulthood (after 12 years old): UGT1A1/1A4, UGT1A1/1A9, UGT1A4/1A6, and UGT1A4/1A9. Conversely, UGT1A4/2B7 and UGT1A9/2B7 only correlate significantly in children under 12 years old. None of the UGT1A and 2B members correlates with UGT3A isoforms, but UGT3A1 and 3A2 are associated with each other ($p=0.028$, $r=0.32$).
Conclusion: We have identified 13 pairs of UGT isoforms that demonstrate statistically significant positive correlations in protein expression. Positive correlations might indicate co-regulation of UGT expression and provides further evidence for cooperation between UGT isoforms in metabolism and clearance. That co-association of isoforms differs with age gives insight into intersection of developmental and genetic regulation of UGT structure and function.

106. *In silico* Homology Modeling of Human UDP-glucuronosyltransferase 1A6 (UGT1A6) reveals new Insights into Structural Folding and Binding of Substrate and Co-substrate

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Purpose: UDP-Glucuronosyltransferase 1A6 (UGT1A6) belongs to the glycosyltransferase (GT) superfamily and uses UDP-glucuronic acid (UDPGA) as co-substrate. It is responsible for metabolism and detoxification of numerous natural compounds and xenobiotics. UGTs have two functional N- and C-terminal domains, with most of the protein residing in the endoplasmic reticulum lumen. A crystal structure of the presumed UDPGA binding region of human UGT2B7 shows high structural similarity to plant and bacterial GTs. No complete UGT structure exists. We aim to produce a new homology model of UGT1A6 to further examine features involved in enzyme function and substrate binding.
Methods: Structural models of human UGT1A6 were produced using I-TASSER with or without a guiding partial crystal structure template (UGT2B7, PDB: 2O6L). Models were analysed and refined using BIOVIA Discovery Studio™. Residues known or predicted to be important for substrate and co-substrate binding were used to define compound binding spheres. Sixty-two compounds were docked using both the Libdock and CDOCKER algorithms, with UGT substrates docked in both the presence and absence of the co-substrate UDPGA.
Results: The highest ranked model (C-score, MODELER, Profiles-3D scores) utilized the guiding template structure (59% aligned sequence identity), and closely matched other GT structures. Root Mean Square Distances (RMSD) over aligned residues ranged from 2.28 (*Medicago truncatula* UGT71G1, sequence ID 16.3%) to 3.55 (*Streptomyces antibioticus* glycosyltransferase OleI, sequence ID 19.2%) prior to full energetic minimization. Models could not be constrained for the presence of membrane, hence transmembrane and C-terminal domains are not accurately localized. Preliminary docking experiments indicate that UDPGA interacts with residues including His371 and Glu379, which are highly conserved and identified as important for

glucuronidation.
Conclusion: Due to extensive functional and structural conservation within the GT superfamily, homology modeling may provide insight into the structure and function of UGTs in the absence of high-resolution crystal structures.

107. Role of Elevated sFLt-1 on the Regulation of Placental Transporters in Women with Pre-eclampsia

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Purpose: Pre-eclampsia (PE), a prominent obstetric complication is associated with elevated levels of sFlt-1, a soluble Vascular Endothelial Growth Factor (VEGF) receptor. However, virtually no information exists on the expression and regulation of human placental transporters in PE. Therefore, our objective was to explore the impact of PE and sFlt-1 on the expression of transporters in human placenta, and elucidate the regulatory mechanism *in vitro.*
Methods: Human placental samples were collected from preterm pregnancies diagnosed with PE (n=34) and were gestational age-matched with samples from preterm pregnancies with no obstetric complications (controls, n=24). Meanwhile, BeWo cells were treated with sFlt-1 alone and with VEGF for 72 hours. Gene expression was measured via qRT-PCR.
Results: A significant 30-50 % downregulation of ABCG2, ABCC1, ABCC2, SLC22A1, SLC22A3, SLC22A11, and SLC29A2 was seen in placentas complicated by PE compared to healthy controls ($p < 0.05$). mRNA levels of sFLT-1 were induced by 2.5 fold in preterm placentas of women with PE, relative to preterm controls ($p < 0.01$). Likewise, BCRP protein expression was significantly downregulated by 50% in PE compared to controls. Administration of sFlt-1in cells resulted in an 85-90% downregulation of ABCG2 transcript levels which was attenuated by VEGF.
Conclusion: Our findings suggest that the protective function of the placenta is compromised during PE with significantly altered the expression of clinically important transporters. Furthermore, our *in vitro* results show that sFlt-1 is involved in the regulation of BCRP in placenta. As this may impact fetal health and development, further studies are needed to determine the impact of PE-induced changes on fetal exposure to their substrates.

CSPT Poster Session 2

Thursday, May 24

CSPT Posters - Session 2

Thursday, May 24

108. Quantification of NSAIDs in Human Tissues with a Novel UHPLC/MS/MS Method

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Background: Nonsteroidal anti-inflammatory drugs (NSAIDs) are analgesics with antipyretic and anti-inflammatory effects. NSAIDs are one of the most commonly used drug classes in the world and this coupled with their side-effect profiles, and contraindications, mean that a method for screening NSAIDs would be valuable in the fields of biomedical and environmental sciences.
Objectives: We aim to develop a method that simultaneously detects the five most common NSAIDs (salicylic acid (SA), diclofenac (DCF), ibuprofen (IBU), indomethacin (IND) and naproxen (NAP)) in biological matrices.
Methods: A novel UHPLC/MS/MS method for the simultaneous quantification of these five NSAIDs using aceclofenac as an internal standard was developed. Pharmacokinetic analysis was performed to determine for how long plasma levels of NSAIDs could be detected after ingestion.
Results: In solvent, the limit of sensitivity is below 1 ng/mL for all samples, with linear range of 1-1000 ng/mL for all analytes except IBU (10 – 1000 ng/mL). Lower limit of quantitation is 1 ng/mL for DCF and SA, 2.5 ng/mL for NAP and 20 ng/mL for IBU and IND. Validation in plasma and other biological matrices is ongoing. After a single oral dose all NSAIDs would be detected within five half-lives (0.4-4.2 days), with SA, IBU and NAP detected for 10 half-lives (0.8-8.3 days). From steady-state, all NSAIDs could be detected 10 half-lives from last dose.
Conclusions: Our UHPLC/MS/MS method can simultaneously quantitate five NSAIDs in human tissues and provides a novel screening tool for these drugs in biological matrices, with numerous applications in health research.
Keywords: Analytical quantitation, NSAIDs, pharmacokinetics, screening, UHPLC/MS/MS

109. Investigating the Mechanisms of Bile Acid-mediated Organ Toxicity in Ntcp (*Slc10a1*) Knockout Mice

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Background: Na+-taurocholate cotransporting polypeptide (NTCP) mediates uptake of conjugated bile acids and drugs from portal circulation into the liver. Published Ntcp knockout mouse data noted hypercholanemia and significant alterations in bile acid transporter mRNA expression in 30-35% of knockout mice. The mechanisms of bimodal phenotypes within the knockout population remain unclear and require further investigation.
Objectives: Aim 1: Identify hypercholanemic and normocholanemic mice in our previously uncharacterized Ntcp knockout mouse model. Aim 2: Quantify expression of proteins involved in bile acid synthesis and transport in hypercholanemic knockout, normocholanemic knockout, and control mice.
Methods: Total serum bile acid levels were quantified using an enzyme-cycling method. Individual serum bile acids will be quantified using LC-MS/MS. Hepatic, renal, and ileal mRNA expression will be quantified using RT-qPCR.
Results: Approximately 25-30% of our Ntcp knockout mice died 4-7 weeks after birth and were noted to have strikingly elevated total serum bile acid levels (464.6 ± 29.5μM) compared to age-

matched controls (3.37 ± 0.71μM). Upon preliminary necroscopy, such knockout mice display severe renal damage secondary to bile acid accumulation.
Conclusion: Bimodal serum total bile acid measurements in our Ntcp knockout mice are consistent with the published findings. We are the first to report lethality of a hypercholanemic subset of Ntcp knockout mice, likely due to bile acid-mediated kidney injury. Using RT-qPCR, we aim to elucidate pathways responsible for morbidity in hypercholanemic mice and, alternatively, for compensation in normocholanemic knockout mice.
Keywords: NTCP, bile acid transport

110. Genome-wide Association Study of Anthracycline-induced Cardiotoxicity in Adult Cancer Patients

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Background: Anthracycline agents, such as doxorubicin and epirubicin, are commonly prescribed for a variety of cancers. Nevertheless, up to 18% of adult patients develop severe life-threatening anthracycline-induced cardiotoxicity (ACT). Clinical risk factors include cumulative anthracycline dose, age, prior thoracic radiotherapy, and pre-existing cardiac disease. Germline genetic variants associated with a higher ACT risk in adults have not been identified.
Objectives: To replicate previous, and discover new, ACT-associated genetic variants in adult cancer patients to improve our understanding of the genetic causes of ACT.
Methods: Genotyping of 1.7 million variants has been performed on 180 adult cancer patients (60 cases, 120 controls) treated with anthracyclines and rigorously assessed for ACT. Targeted and genome-wide analyses will be performed using logistic regression, including significantly-associated clinical variables as covariates, to explore the role of known and novel ACT-associated variants. Functional and biological relevance of candidate variants will be examined using computational annotation tools such as VEP, GTEx, and CADD, and associated genes will be investigated for enrichment in specific pathways.
Results: An extensive review of the literature has identified 20 genes that have been previously associated with ACT, the role of which will be validated in our cohort through a targeted analysis. We will present the top candidate variants that reach statistical significance in both targeted and genome-wide analyses.
Conclusions: The identification of genetic variants associated with ACT will play an important role in improving the safety of anthracyclines and, ultimately, in reducing the burden on the healthcare system as well as affected patients.
Keywords: Pharmacogenomics, Anthracyclines, Cardiotoxicity, GWAS

111. Physician Feedback and Antibiotic Prescribing Patterns

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Background: Antibiotics have revolutionized modern medicine and have transformed infections with serious potential morbidity and mortality into eminently manageable and survivable conditions. However, in addition to the direct unnecessary costs from dispensing redundant therapy, inappropriate antibiotic prescribing incurs substantial indirect socio-economic costs related to the associated adverse side-effects and the promotion of the development of resistant organisms. Audit and feedback (A&F) when well designed, presented, framed and implemented, has been shown to be a cost-effective and efficacious tool in influencing physician behaviour change.
Objectives: Assess the impact of audit and feedback in antibiotic prescribing patterns
Methods: A literature review was conducted on Pubmed, searching for articles using the search

terms “prescriptions”, “prescribers”, “antibiotic”, “audit and feedback” and “inappropriate prescribing”.
Results: Four studies were identified for inclusion. An important distinction between effective and ineffective audit and feedback interventions in antibiotic prescribing is related to the method and context of framing an individual physician’s behavior. When framed in context, audit and feedback has been shown to decrease inappropriate antibiotic prescribing.
Conclusions: As the gate-keepers to antibiotic prescriptions, targeting physician perception and behavior with A&F has been shown in American and British settings to be effective at altering prescribing patterns. Given the incidence of inappropriate antibiotic prescribing in Canada and the consequent adverse socio-economic and medical outcomes, there is a need to target and alter Canadian physician antibiotic prescribing behavior. Audit and feedback is imminently applicable to the Canadian context and, if implemented well, would yield widespread and long-term societal benefit
Keywords: Audit, feedback, antibiotic prescribing, physician

112. Safety of laninamivir Octanoate, a Neuraminidase Inhibitor, in Lactating Women with Influenza

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Background: Both pregnant and lactating women are thought an important group to be treated with anti-influenza virus drugs once they are symptomatic during flu season. Laninamivir octanoate (LO / Inavir®, Daiichi Sankyo Company, Limited), one of neuraminidase inhibitors, was developed in Japan and has been on the market for 7 years. Information on safety of the medication use in the group, especially lactating women, is insufficient.
Objectives: To assess whether LO is safe to use in lactating women, the concentration of LO and its active metabolite, laninamivir (LA), in breast milk samples from patients who were diagnosed as influenza and inhaled 40mg of LO once.
Methods: Each patient was asked to milk a couple of times after inhaling LO, to keep them in their refrigerators at home, and to bring them to the clinic after recovery. Fifty μL of each milk sample was pretreated by solid phase extraction method using OASIS MCX (3cc/60mg), followed by measuring concentration of LO and LA in breast milk with liquid chromatography-tandem mass spectrometry at Pharmacokinetics and Bioanalysis Center, Shin Nippon Biomedical Laboratories, LTD. The detection limit of both LO and LA is 1 ng/mL.
Results: Twenty-seven pumped milk samples (half an hour to 48 hours after inhalation) from 5 patients were examined. None of them showed LO / LA level over the detection limit.
Conclusions: Available data suggest that inhaled LO by a lactating mother does not affect her baby via breast milk, and seems safe.
Keywords: Laninamivir octanoate, Influenza, lactating women, breastfeeding, safety

113. Single Time Point Sampling for Assessment of Fexofenadine as an *In Vivo* Drug Transporter Probe

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Background: In vivo probe substrates are used to assess activity of hepatic metabolism and transport to help delineate effects of disease and drug-drug interactions on drug disposition. For example, the non-sedating anti-histamine fexofenadine, is effective as a nonselective transporter probe but is limited in clinical use due to its relatively long half-life (11-16 hours). Many patient groups are unable to undergo full PK characterization due to the large time commitment.
Objectives: This study investigated relationships between fexofenadine exposure, area under the curve (AUC), and single time point fexofenadine concentration. We hypothesized that a single time

point measurement would provide a good estimate of fexofenadine exposure.
Methods: Data was utilized from two published studies that orally administered 120 mg of fexofenadine. Nolin et al. (S1) and Thomson et al. (S2) collectively studied 18 healthy controls and 24 chronic kidney disease (CKD) patients. Serial blood samples were drawn over 8 or 12 hours for S2 or S1, respectively. Linear regression was performed using 1, 2, 3, and 4-hour time points plotted against $AUC_{0\rightarrow\infty}$ (S1) or $AUC_{0\rightarrow 8}$ (S2).
Results: For S1, linear regression yielded R^2 of 0.77, and 0.88 for 3-hour and 4-hour time points, respectively ($p<0.0001$). Comparably, for S2, 3-hour and 4-hour time points yielded R^2 of 0.95, and 0.95 ($p<0.0001$).
Conclusions: Single-time point measurements of fexofenadine are correlated to exposure when taken at 3 or 4 hours following dosing, including CKD patients. Ongoing research is utilizing single time point measurements to determine dialysis-mediated changes in fexofenadine exposure in CKD patients.
Keywords: Chronic kidney disease (CKD), fexofenadine, drug disposition, drug transport

114. Development of a Novel Cellular Reporter Assay to Measure Anticholinergic Activity

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Background: Anticholinergic activity is an important contributor to serious adverse drug events, especially in older adults. This has led to the development of numerous scales to quantify anticholinergic activity; to date these have failed to garner widespread acceptance due to their subjective nature.
Objectives: The objective of this study was to develop a cellular reporter assay that could quantitatively measure anticholinergic activity.
Methods: The DiscoverX PathHunter® β-Arrestin eXpress GPCR Assay was used. This assay contains human cells expressing the muscarinic 1 receptor engineered to give off light when bound by an agonist. The assay was used to identify cholinergic agonist binding and anticholinergic inhibition of agonist binding. The muscarinic agonist used was acetylcholine, and the anticholinergic agents investigated included; atropine, digoxin, famotidine, and ranitidine. Each agent was assessed across a range of concentrations. A standard luminescence plate reader (Biotek SynergyHT) was used to measure light emitted at all wavelengths. Statistical analysis was completed using GraphPad Prism 5.
Results: We used the muscarinic 1 receptor based assay to examine acetylcholine agonism and calculated the EC50 as 9778 nM. Subsequent trials to investigate inhibition of the acetylcholine induced luminescence at a concentration corresponding to the EC80 (115 600 nM) showed complete inhibition by atropine at a concentration of $2.73x10^{-5}$ M and partial inhibition by varying concentrations of digoxin, famotidine, and ranitidine.
Conclusions: A cellular reporter assay can be used to measure anticholinergic activity. This objective measure of anticholinergic activity may be helpful to predict anticholinergic burden and help direct drug-therapy decisions.
Keywords: Anticholinergic, GPCR assay, muscarinic 1 receptor

115. Swelling-induced Chloride Current in Glioblastoma Proliferation, Migration and Invasion

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Background: Glioblastoma (GBM) remains the most common and aggressive malignant brain tumor originating in the central nervous system. Diagnosis is lethal with a median survival of <15 months. Aberrant swelling-induced chloride channel $I_{Cl,swell}$ expression has been linked to GBM cellular functions (i.e. proliferation, migration and invasion).
Objectives: We hypothesize that inhibition of the swelling-induced chloride channel $I_{Cl,swell}$ suppresses GBM cellular functions. The purpose is to establish $I_{Cl,swell}$ as a potential drug target by evaluating DCPIB, a specific antagonist for the swelling-induced chloride channel $I_{Cl,swell}$, on GBM cellular

functions.
Methods: We used the human GBM cell lines U251 and U87. First, with the whole-cell patch-clamp technique to measure activity of $I_{Cl,swell}$. GBM proliferation and viability were assessed with MTT and colony formation assays. Moreover, GBM migration and invasion were assessed with scratch wound and Matrigel invasion assays, respectively. With Western immunoblots, we also assessed in GBM the protein levels of p-Akt/t-Akt, p-JAK2/t-JAK2, and p-STAT3/t-STAT3 in order to examine the underlying mechanism.
Results: We demonstrated that DCPIB enhanced the endogenous swelling-induced chloride channel $I_{Cl,swell}$. GBM proliferation and viability were reduced with DCPIB treatment. DCPIB also suppressed GBM migration and invasion. We found that DCPIB inhibited the JAK/STAT as well as the PI3k/Akt signaling pathways, which could potentially be the underlying swelling-induced chloride channel $I_{Cl,swell}$-dependent mechanism.
Conclusions: Because potentiated swelling-induced chloride channel $I_{Cl,swell}$ activity contributes to the devastating proliferative, migratory and invasive characteristics of GBM, our study establishes the involvement of $I_{Cl,swell}$ in GBM cellular functions.
Keywords: Glioblastoma, $I_{Cl,swell}$, DCPIB

116. Hypoxic Stimulation of Vasoreparative Functions in Human $CD34^+$ Cells is Mediated by Angiotensin Converting Enzyme-2 and Mas Receptor

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Background: $CD34^+$ hematopoietic stem/progenitor cells (HSPCs) have the propensity of re-endothelialization and vascular regeneration. Angiotensin Converting Enzyme-2 (ACE2) generates the heptapeptide, Angiotensin (Ang)-(1-7), which produces vasoprotective effects by acting on Mas receptor (MasR). We have previously reported that hypoxia stimulated vasoreparative functions of $CD34^+$ cells, which was impaired in MasR-deficient murine HSPCs.
Objectives: Current study tested the hypothesis that hypoxic stimulation of HSPC functions are mediated by ACE2 and MasR.
Methods: $CD34^+$ cells were isolated from mononuclear cells (MNCs) derived from healthy volunteers. Protein and mRNA expressions of ACE2 and MasR were determined in cells after exposure to normoxia (20% O_2) or hypoxia (1% O_2). $CD34^+$ cells were transduced with lentiviral particles (LV) carrying either ACE2-, MasR- or scramble-3'-UTR fused downstream to firefly luciferase reporter gene.
Results: Hypoxia stimulated mRNA and protein expressions of ACE2 and MasR in $CD34^+$ cells, but not in MNCs. In the presence of hypoxia-inducible factor-1α (HIF-1α) inhibitor, hypoxic upregulation of ACE2 or MasR was not observed. Luciferase activity was increased by hypoxia, compared to normoxia, in either ACE2- or MasR-luciferase expressing cells. Co-transfection experiments using ACE2 and MasR specific miRNA (miR-421 or miR-143 for ACE2 and MasR, respectively) confirmed that the observed luciferase activity in both normoxic and hypoxic condition was dependent on ACE2 or MasR, respectively.
Conclusions: Collectively, these results provide compelling evidence for the hypoxic upregulation of ACE2 and MasR in $CD34^+$ cells, which largely contribute to the revascularization of ischemic areas following vascular injury.
Keywords: $CD34^+$ cells; Stem/progenitor cells; Hypoxia; MicroRNA; ACE2

117. Characterization of the Metabolome and Renal Tubular Cisplatin Disposition in Cisplatin Induced Acute Kidney Injury

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Background: Cisplatin-induced acute kidney injury (AKI) is diagnosed by increased serum creatinine (SCr), but nephrotoxicity develops before rises in SCr are detectable. Novel diagnostic/predictive markers of AKI may explain why approximately 1/3 of cisplatin patients get AKI while others do not. FVB/N mice have greater susceptibility to cisplatin-AKI than C57BL/6 mice and we used these strains to model the variability of cisplatin nephrotoxicity.
Objectives: 1) Determine the effects of AKI on expression of renal transporters and enzymes involved in cisplatin disposition; 2) Investigate metabolic differences between FVB/N and C57BL/6 mice using metabolomics.

Methods: FVB/N and C57BL/6 mice were treated with 15 mg/kg cisplatin or saline. Mice were sacrificed 1 or 3 days following treatment; gene expression was assessed using RT-PCR, and LC-MS was used for untargeted metabolomics.
Results: Renal expression of uptake transporter Oct2 and metabolizing enzyme Ggt1 were 20% and 45% higher, respectively, in FVB/N mice compared to C57BL/6 ($p<0.05$). Ggt1 expression was lower in day 1 and 3 cisplatin-treated FVB/N compared to saline (-44% and -50% respectively, $p<0.05$). Principle component analysis (PCA) of mouse plasma and kidney samples demonstrated metabolic differences attributed to both strain and cisplatin treatment.
Conclusions: mRNA expression of Oct2 and Ggt1 in FVB/N mice was higher compared to C57BL/6. PCA separation of untreated mice indicates strain metabolic differences, while separation by treatment groups suggests that cisplatin alters the metabolic profiles of the mice. Our data suggests differences in expression of cisplatin transporters/metabolizing enzymes, and metabolic profiles may explain strain dependent differences in susceptibility to cisplatin-AKI.
Keywords: Metabolomics, acute kidney injury, cisplatin, biomarkers

118. Viral Mimetic Imposes a Dysregulation of Nutrient and Neurotransmitter Transporter Expression in Rat Placenta

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Background: Previous research has shown that inflammation during late gestation can cause changes in the expression of ATP-Binding Cassette and Solute Carrier transporters located in the placenta. It is unknown whether transporter dysregulation also occurs during inflammation at mid-gestation, a critical time for fetal neurodevelopment.
Objective: To determine whether viral infection during pregnancy impacts the expression of key placental nutrient and neurotransmitter transporters at a time critical for fetal neurodevelopment.
Methods: Pregnant Sprague-Dawley rats were injected intraperitoneally with poly(I:C) (10 mg/kg) on gestational day 14. After 24 hours, dams were sacrificed and placentas were collected. The expression of key nutrient and neurotransmitter transporters was examined using qRT-PCR and Western blotting.
Results: Poly(I:C) induced a 1.7-fold increase in TAUT (Slc6a6) mRNA ($p < 0.05$). This induction was accompanied by a trend towards a 1.6-fold increase in TAUT protein expression ($p = 0.0617$). mRNA levels of PCFT (Slc46a1) were also significantly upregulated 1.2-fold ($p < 0.05$). A trend towards increased mRNA expression was observed for LAT1 (Slc7a5, $p = 0.1502$) and BGT1 (Slc6a12, $p = 0.0999$).
Conclusions: Simulating viral infection during mid-gestation in rats causes dysregulation of the expression of nutrient and neurotransmitter transporters in the placenta. Since these transporters have substrates involved in critical aspects of fetal neurodevelopment, their dysregulation may alter fetal access to these substrates which could have deleterious effects on fetal outcomes.
Keywords: Inflammation, transporters, pregnancy, placenta, fetal outcomes

119. Impact of MS-induced Systemic Pro-inflammatory Cytokines on the Regulation of Human Placental Transporters

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Background: Placental drug transporters play a crucial rule in the transfer of nutrients to the fetus and protection against xenobiotics. While preclinical and clinical studies have shown that systemic inflammation cause dsyregulation of placental drug transporters, the impact of elevated systemic levels of the pro-inflammatory cytokines, IL-17, IL-22 and IL-23 associated with MS, has not been studied. We hypothesize that MS associated cytokines will impact the expression of placental drug transporters.
Objective: To examine the impact of IL-17, IL-22 and IL-23 on the expression of key placental transporters *in vitro* in a human trophoblast cell line.
Method: BeWo cells were grown to 80% confluency. IL-17, IL-22, and IL-23 were added to the cells at various concentrations (0, 0.5, 1, 10, 50,100 ng/ml) for periods of 24, 48 and 72 hr. qRT-PCR was used to measure the gene expression of BCRP, MDR1, MRP1, MRP2, OATP2B1, OAT4.
Results: As compared to controls, IL-17

significantly decreased the mRNA of BCRP and MRP2 after 24h ($p<0.001$) and increased levels of OATP2B1 after 24 and 72hr ($p<0.01$). IL-22 significantly decreased the BCRP and OAT4 genes ($p<0.01$) after 48 and 72 hours respectively. Likewise, IL-23 significantly downregulated the mRNA levels of OAT4 and OATP2B1 at 24 and 48hr, respectively ($p<0.01$).

Conclusion: Exposure of human placental cells to IL-17, IL-22 and IL-23 imposed alterations in the expression of many clinically important placental drug transporters. As these cytokines are elevated in MS patients, they potentially impact fetal exposure to their substrates.

Key words: multiple sclerosis, systemic inflammation, placental drug transporters

120. Low-dose, Low-fluctuation Dihydropyridine Concentrations as Delivered by Nifedipine-Extended-release Tablets Do not Perturb Heart Rate

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Background: Dihydropyridine agents are highly effective in antihypertensive therapy, with amlodipine and nifedipine-extended-release (NXL) being the most commonly used. Tachycardia caused by administration of nifedipine is highlighted in older literature, but relates to formulations used prior to NXL. Despite longstanding evidence that NXL has no effect on sympathetic activity (de Champlain J Hypertens 1998; 16: 1357), elevation of heart rate (HR) is still cited as a consideration to avoid use of NXL.

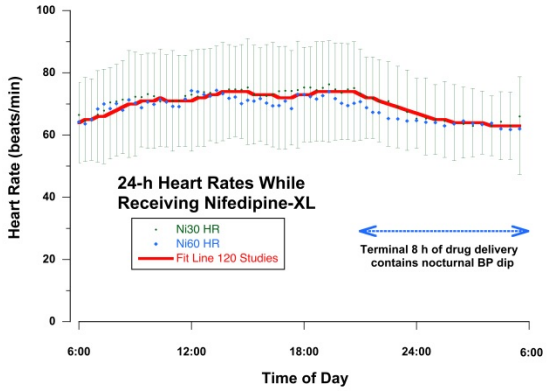
Objectives: To examine the effects of NXL on HR in data collected from 120 uniformly conducted ambulatory blood pressure monitoring (ABPM) studies.

Methods: HR data were analyzed from 24-h ABPM studies conducted twice in 60 pts to examine systolic blood pressure (SBP) response to morning doses of 2 differing NXL formulations of 30 mg or 60 mg tabs.

Results: Mean HR ranged between 63-76 bpm on 30 mg/d, and 62-74 bpm on 60 mg/d with tight standard deviation ranges (Fig HR mean ± SD).

Conclusions: Sympathetic tone increases in response to the rapid declines in SBP associated with rapidly increasing dihydropyridine concentrations. There was no evidence of drug-induced tachycardia following NXL morning dosing, consistent with the lack of sympathetic activation observed by de Champlain. Doubling the dose did not increase HR, consistent with both doses producing concentrations < minimum required to effect rapid change in SBP. However, NXL retains its short half-life, allowing more rapid titration and discontinuation.

Keywords: Nifedipine, Hypertension, Sympathetic Response.



121. Identifying the role of G-Protein Signalling Modulator 3 in GPCR signalling

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Background: G protein coupled receptors (GPCRs) are the largest superfamily of mammalian cell surface receptors and serve as targets for over 30% of current pharmaceuticals. GPCRs activate G protein heterotrimers (Gα•GDP/Gβγ) by promoting GDP dissociation and GTP association. GPCR signalling is limited via G protein activity and interactions with β-arrestins. G Protein Signalling Modulator-3 (GPSM3) is a novel protein that

influences receptor signalling by binding to inactive $G\alpha_i$-GDP, limiting GDP dissociation from $G\alpha_i$ and also preventing $G\alpha_i$ re-association to the $G\beta\gamma$ subunit. GPSM3 thus has the potential to prevent $G\alpha_i$-mediated signalling while prolonging $G\beta\gamma$ signalling.

Objectives: To determine whether GPSM3 inhibits GPCR signalling.

Methods: Real-time bioluminescence-based kinetic assays for cAMP production and β-arrestin recruitment were used to study the effects of GPSM3 and mutants thereof on GPCR signalling in transiently transfected HEK-293H cells.

Results: GPSM3 overexpression inhibited basal and agonist-stimulated β-arrestin recruitment to $G\alpha_i$-coupled α_{2A}-adrenergic and μ-opioid receptors by 52% ($p<0.0001$), with no effect on recruitment to G_s- or $G_{q/11}$-coupled GPCRs. The effect of GPSM3 on α_{2A}-adrenergic-β-arrestin diminished with partially inactive mutants of GPSM3 ($p<0.001$) and not observed with fully inactive mutants. In cAMP assays, GPSM3 reduced forskolin potency on endogenous HEK-293H adenylyl cyclase activity ($LogEC_{50}$=-5.261) when compared with control ($LogEC_{50}$=-5.916), but the reason for this decrease is unclear ($p<0.0001$).

Conclusions: The selective effect of GPSM3 on β-arrestin binding to G_i-coupled receptors is consistent with its greater affinity for $G\alpha_i$ relative to other G protein subtypes, and suggests that G protein activation may be a necessary step in GPCR-β-arrestin recruitment.

Keywords: G-Protein Signalling Modulator-3, GPCR, adenylyl cyclase, β-arrestin

122. Comparing Pharmacokinetics of All-*trans* Retinoic Acid Between Adults and Children with Acute Promyelocytic Leukemia

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Background: All-*trans* retinoic acid (ATRA) is a key drug of differentiation therapy for acute promyelocytic leukemia (APL). ATRA toxicity is well known to include differentiation syndrome and neurotoxicity. The pharmacokinetics of ATRA has been reported previously, but the comparison of pharmacokinetics parameters between different ages has not been performed.

Objectives: We evaluated the relationship between the pharmacokinetics of ATRA and central nervous system (CNS) toxicity in children and adults with APL.

Methods: Six children (9.3±2.4 year-old) and eight adults (35.5±13.3) with APL were enrolled. All of patients received oral ATRA (45 mg/m^2 per day) and chemotherapy, and all of them achieved complete remission. The pharmacokinetics of ATRA was determined within one week of starting therapy.

Results: The Cmax values of the children (352.0±173.6 ng/ml) were higher than those of the adults (203.9±34.5), but the other parameters (AUC, half-life time, clearance, and volume of distribution) did not differ between these two age groups. Two children suffered from CNS toxicities but none of the adults had CNS toxicity.

Conclusions: The bioavailability of ATRA was not different in adults and children. The children had higher Cmax values than the adults. The pharmacokinetic parameters of the children with CNS toxicity were not different from those of the children without CNS toxicity. The incidence of CNS toxicity in children is higher than adults although its bioavailability between both groups is similar. Further studies are needed to determine the optimum regimen for ATRA combined with chemotherapy in children with APL, in order to reduce ATRA - related neurotoxicity.

Keywords: all-*trans* retinoic acid, acute promyelocytic leukemia, pharmacokinetics

123. Insights into PAR4 Signaling and Biased Agonism

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Background: Proteinase-activated receptor 4 (PAR4) is a G-Protein Coupled Receptor activated following proteolytic cleavage of the receptor N-terminus by enzymes such as thrombin, trypsin, and Cathepsin-G. Proteolysis reveals a receptor activating motif termed the tethered ligand (TL) which binds intramolecularly to trigger receptor signaling cascades. Synthetic peptides derived from the TL sequence can also activate PAR4. Here we examined PAR4 signaling following activation with

a library of TL derived peptides to identify compounds with novel pharmacological properties.
Objectives: To identify novel PAR4 activating peptides that exhibit functional selectivity for beta-arrestin or Gαq coupled signaling pathways.
Methods: The synthetic agonist peptide (AYPGKF-NH2) and 35 novel derivatives of PAR4 agonist peptides were synthesized (<95% purity) using solid phase Fmoc-peptide chemistry, purified by preparative high performance liquid chromatography (HPLC), and characterized by liquid chromatography mass spectrometry (LC-MS). We used calcium sensitive fluorescent dyes to monitor elevations in intracellular calcium levels (Gαq coupled), Bioluminescence Resonance Energy Transfer (BRET) to monitor beta-arrestin-1 and -2 recruitment, and western blotting to determine activation of p44/42 MAPK and Akt following receptor activation.
Results: 22 of 35 peptides showed decreased beta-arrestin recruitment compared to AYPGKF-NH2. A subset of peptides also showed decreased calcium signaling compared to AYPGKF-NH2. Interestingly we identified 7 peptides that recruit beta-arrestins-1 and -2 but are unable to trigger PAR4-dependent calcium signaling.
Conclusions: We have identified novel biased peptide agonists for PAR4 and further work is underway to understand the structural basis for this bias and to understand the physiological consequence of biased signaling through PAR4.
Keywords: Proteinase activated receptor 4 (PAR4), G-protein coupled receptor (GPCR), Biased agonism,

124. Pharmacogenomics of Vincristine-induced Peripheral Neuropathy Implicates Pharmacokinetic snd Inherited Neuropathy Genes

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Background: Vincristine is an effective chemotherapeutic drug that is used to treat various cancers, including acute lymphoblastic leukemia (ALL). Unfortunately, clinical utility is restricted by dose-limiting neurotoxicities that include sensory and motor neuropathies. The identification of pharmacogenomic markers for vincristine-induced peripheral neuropathies (VIPN) is valuable to predict individual susceptibility to this adverse event.
Objectives: We sought to determine the association of VIPN with: a recently-identified risk variant, *CEP72* rs924607, as well as pharmacogenomic variants from drug absorption, distribution, metabolism, and excretion (ADME) genes.
Methods: Pediatric ALL patients were recruited from seven healthcare centres across Canada and were retrospectively graded for VIPN using an intervention-based grading scale. Patients were genotyped for *CEP72* rs924607 and 7,907 ADME genetic variants. This was followed by a meta-analysis of pharmacogenomic data from over 500 patients.
Results: Sex, vincristine duration, and use of nifedipine differed significantly between VIPN cases and controls. *CEP72* rs924607 was significantly associated with VIPN (P=0.02, OR 3.4). Top ADME variants included *ABCC1* rs3784867 (P=5.34 x 10^{-5}, OR 4.9), and *SLC5A7* rs1013940 (P=9.00 x 10^{-4}, OR 8.6); genes involved in vincristine transport and inherited neuropathy, respectively. The meta-analysis identified an association with an expression quantitative trait locus-related variant for *TTPA* (rs10504361: P=6.85 x 10^{-4}, OR 2.0), a gene associated with a heritable neuropathy-related condition.
Conclusions: By confirming that *CEP72* rs924607 contributes towards VIPN risk in pediatric ALL, our analysis provides essential corroboratory evidence for this biomarker. Further, this study provides evidence for the role of drug transporter and inherited neuropathy genes in VIPN.
Keywords: Adverse drug reactions; cancer; pharmacogenomics

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