Conference 2016:

From Drug Discovery to Health Outcomes: Population to Patient

May 31 - June 3, 2016
River Rock Resort, Richmond, BC Canada

A joint conference of:

Canadian Society for Pharmaceutical Sciences
Canadian Chapter of Controlled Release Society

Conference Chair:
Frank Abbott, University of British Columbia, Vancouver, BC

Conference Organizing Committee:
Michael Coughtrie (UBC), Jason Crawford (Centre for Drug Research & Development), David Kwok (BRI Biopharmaceutical Research Inc.), Shyh-Dar Li (UBC), Larry Lynd (UBC), Corey Nislow (UBC), Simon Pimstone (Xenon Pharmaceuticals Inc.), Robert Young (Simon Fraser University)

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Conference Program

TUESDAY, MAY 31, 2016	
8:00 AM	***Registration***
9:00 - 5:00	**Industry Day: Innovation and Management of Modern Pharmaceuticals** ***(Whistler Ballroom B)***
9:00 - 10:00	**PLENARY 1: Carolyn Buser-Doepner**, GSK ***New Trends in Pharma-Academia Collaborations for Drug Discovery*** *Chair: Amyn Sayani, GSK* **SPONSORED BY: COLORCON**
10:00-10:15	***Refreshment and networking break***
10:15 - 11:00	**Showcasing Drug Discovery Companies** *Chair: Jason Crawford, CDRD* **Robin Sherrington**, Xenon Pharmaceuticals *Human Channelopathies: Providing Key Insights Into Drug Development* **Ernie McEachern**, Alectos Therapeutics *Alectos Therapeutics: Targeted Innovation in Preclinical Drug Discovery*
11:00 - 12:30	**Novel Delivery Technologies for Therapeutics** *Chair: Pieter Cullis, UBC* **John Babcook**, Zymeworks Inc. *Zymelink™ - Next Generation Drug Conjugates* **James Taylor**, Precision Nanosystems *The NanoAssemblr Platform: Microfluidic-based Manufacture of Nanomedicines from uLs to 10s L* **Michael Hope**, Acuitas Therapeutics *A Lipid Nanoparticle Platform to Enable mRNA Therapeutics*
12:30 - 1:30	***Lunch break and networking***
1:30 - 2:30	**Pharma at the Forefront in Drug Discovery** *Chair: Robert Young, SFU* **Jennifer Yearley**, Merck Research Labs *Translational Biology in the IO Space - Patient Response, Combination Therapies, New Approaches* **Anne Fourie**, Janssen Pharmaceutical Research & Development *Psoriasis - From Transformational Treatments to Cure and Interception*
2:30 - 3:00	***Refreshment and networking break***
3:00 - 4:30	**New Commercialization Strategies, Regulatory Challenges, Big Data Issues** *Chair: Jason Crawford, CDRD* **David Main**, Aquinox, & Chair BIOTECanada *New Commercialization Strategies* **Farzad Ali**, Pfizer *Access to New Medicines, Do Canadians Deserve Better?* **Paul Terry**, PHEMI Health Systems *Privacy, Governance & Innovation in the Era of Big Data*
4:30 - 5:30	**Closing Plenary: Chris Halyk**, President, Janssen Inc. ***Are Innovative Medicines and our Life Sciences Industry at Risk in Canada?*** *Chair: Catherine Lau, Janssen Inc.*
5:30 - 7:00	***Welcome Reception: CSPS, CC-CRS, AFPC*** ***SPONSORED BY JANSSEN INC.***

WEDNESDAY, JUNE 1 - MORNING SESSIONS		
7:00 AM	***Registration and Poster Set-Up***	
7:30 - 9:00	**Trainee Mentoring Breakfast**	
9:00 - 10:00	**PLENARY LECTURE: Aaron Schimmer, Princess Margaret Cancer Centre** *New Therapeutic Strategies to Target the Mitochondria in Leukemia* *Chair:* Corey Nislow, UBC	
10:00 - 10:30	***Refreshment Break: Posters, Exhibitors, and Networking (Theatre)***	
10:30 - 12:00	**SESSION 1: Special Populations** *Chair*: Abby Collier, UBC ***(Whistler Ballroom A)***	**SPONSORED BY: SANDOZ CANADA** **SESSION 2: Regulatory Challenges and Opportunities** *Chair*: Fakhreddin Jamali, University of Alberta ***(Whistler Ballroom B)***
10:30	*Pediatric Development of Metabolizing Enzymes* **Abby Collier**, University of British Columbia	*Regulatory Issues on the Determination of Bioequivalence for Modified-Release Drug Products with Multiphasic Concentration Profiles* **Laszlo Endrenyi**, Faculty of Medicine, University of Toronto
11:00	*PBPK Modelling and Simulation in Pediatric Drug Development* **Andrea Edginton**, University of Waterloo	*Current Status of Decision-making for Biosimilars in Canada* **Agnes Klein**, Biologics and Genetics Therapy Directorate, Health Canada
11:30	*Developmental Pharmacology – ADME Consequences in Children* **Catherijne Knibbe**, Universiteit Leiden	*Challenges in Ensuring Drug Product Quality in the Product Lifecycle* **Krishnan Tirunellai**, Therapeutic Products Directorate, Health Canada
12:00 - 12:30	**GSK/CSPS Early Career Award Lecture** **Mary De Vera, UBC** *Patient Engagement in Medication Adherence Research* *Chair: Larry Lynd, UBC*	
12:30 - 2:00	***Lunch break*** ***Posters, Exhibitors, and Networking (Theatre)***	

WEDNESDAY, JUNE 1 - AFTERNOON SESSIONS		
2:30 - 5:10	**SESSION 3: Nanomedicines Become Personal: Opportunities and Challenges** *Co-Chairs*: Shyh-Dar Li, UBC, and Amy Lee, Arbutus Biopharma ***(Whistler Ballroom A)***	**SESSION 4: Broaching the Fourth Hurdle: Getting Drugs on the Formulary** *Chair*: Larry Lynd, UBC ***(Whistler Ballroom B)***
2:30	*Image-guided Focused Ultrasound for Targeted Delivery of Drugs* **Kullervo Hynynen**, Sunnybrook Res. Institute	*(2:30) Orphan Drugs-Catastrophic Drug Coverage* **Fred Horne**, Horne and Associates
3:00	*Personalize Nanomedicines by Developing Multifunctional Nanoparticles and Identifying Therapeutic Biomarkers* **Shyh-Dar Li**, UBC	*(2:45) Developing Specialty Drugs for a Conditional Reimbursement Environment: Is Quicker Necessarily Better?* **Chris McCabe**, University of Alberta
3:30	***Refreshment Break: Posters, Exhibitors, and Networking (Theatre)***	
4:00	*Porphysome Nanotechnology: Discovery and Road to Clinical Translation* **Gang Zheng**, Ontario Cancer Institute	*(3:00) Perspectives from a Public Drug Plan on the Challenges and Opportunities with Expensive Drugs for Rare Diseases (EDRD)* **Eric Lun,** B.C. Ministry of Health
4:30	*TKM-Ebola and TKM-Ebola-Guinea: Rapid Re-development of a Nucleic Acid Therapeutic in Response to the West Africa Outbreak* **Amy Lee**, Arbutus Biopharma Corporation	*(3:15) The Complexity in Making Reimbursement Decisions around Expensive Drugs for Rare Diseases* **Doug Coyle**, University of Ottawa
		(4:00 - 5:00) Panel Discussion
5:00 - 5:15	**Oral Presentation from Posters:** *Polymer-Lipid Based Nanomedicine of Synergistic Drug Combination for Improving Chemotherapy of Multidrug Resistant Breast Cancer* **Rui Xue Zhang**, University of Toronto	**Oral Presentation from Posters**: *Preferences for Donating Money to Support Drug Development Research Projects in a Sample of Canadian and U.S. Adults* **Nick Dragojlovic**, University of British Columbia
5:15 - 6:00	***Posters, Exhibitors, and Networking (Theatre)***	

THURSDAY, JUNE 2 - MORNING SESSIONS		
7:00 AM	***Registration and Poster Set-up***	
7:30 - 9:00	**Breakfast Lectures: *Medical Marijuana*** *Chair*: Frank Abbott, UBC **Jonathan Page**, UBC *Chemical and Genomic Analysis of Cannabis* **Caroline MacCallum,** Greenleaf Medical Clinic, & UBC Hospital Medical Clinic, Vancouver *Medical Cannabis and Cannabinoids*	
9:00 - 10:00	**PLENARY LECTURE: Ivana Cecic , Genome BC** *Genomics in Canada: From Knowledge Generation to Patient Outcomes* *Chair*: Corey Nislow, UBC	
10:00-- 10:30	***Refreshment Break: Posters, Exhibitors, and Networking (Theatre)*** ***BREAK SPONSORED BY MSFHR***	
10:30 - 12:00	**SPONSORED BY: GENOME BC** **SESSION 5: Pharmacogenomics in the Clinic and Community** *Chair*: Corey Nislow, UBC ***(Whistler Ballroom A)***	**SESSION 6: Responsive Drug Delivery Systems** *Co-Chairs*: Todd Hoare, McMaster University and Marc Gauthier, INRS ***(Whistler Ballroom B)***
10:30 *11:00* *11:30*	*Harnessing the Power of Synthetic Lethality: Identifying and Targeting Dependencies in Cancer* **Lisa Belmont**, Genentech *Implementation of Pharmacogenomics for the Prevention of Severe Adverse Drug Reactions in Pediatric Oncology* **Colin Ross,** UBC and CFRI *UBC - GenomeBC - BCPhA Project* **Corey Nislow**, UBC	(10:30-10:40) **Trainee Presentation**: *Complete Regression of Xenograft Tumors upon Targeted Delivery of Paclitaxel via Π-Π Stacking Stabilized Polymeric Micelles* **Roy van der Meel**, Utrecht University / UBC *Smart Automated Release, Because Drugs Don't Work in Patients who Don't Take Them* **Adah Almutairi**, University of California, San Diego *Poly(2-oxazoline) Biomaterials* **Richard Hoogenboom**, Ghent University, Belgium *"Bio-hybrid" Therapeutics* **Marc Gauthier**, Institut National de la Recherche Scientifique (INRS)
12:00 - 12:30	**CSPS Lifetime Achievement Award Lecture** **Fakhreddin Jamali, University of Alberta** *Pharmaceutical Research and Development, Lessons Learned* *Chair: Raimar Loebenberg* ***(Whistler Ballroom A)***	
12:30 - 2:30	***12:30 - Annual Meetings: CSPS (Ballroom A) & CC-CRS (Ballroom B)*** ***Lunch Break*** ***Posters, Exhibitors, and Networking (Theatre)***	

THURSDAY, JUNE 2 - AFTERNOON SESSIONS			
2:30 - 5:00	**SPONSORED BY: ZYMEWORKS** **SESSION 7: Drug Targeting and Targeting Drugs** *Chair*: Robert Young, SFU ***(Whistler Ballroom A)***	**SESSION 8: Health Sustainability Evidence** *Chair*: Mark Harrison, UBC ***(Whistler Ballroom B)***	**SESSION 9: JOINT Session with AFPC** *Chair*: Simon Albon, UBC ***(Fraser Room)***
2:30	*Targeted and Stimuli-sensitive Combination siRNA/Drug Nanopreparations for Multidrug Resistant Cancer* **Vladimir Torchilin,** Northeastern University	*Role of Patient Reported Outcome Measures (PROMs) in the Ongoing Evaluation of Treatment and Reimbursement* **Stirling Bryan**, UBC/Centre for Clinical Epidemiology & Evaluation (C2E2)	*Integrating Pharmaceutical Sciences into a Pharm D Curriculum* **Scott Singleton**, The University of North Carolina at Chapel Hill
3:00	*Advancements in Antibody Drug Conjugate Technology* **Django Sussman**, Seattle Genetics, Inc.	*Patient Reported Outcome Measures (PROMs) and Patient Decision Making* **Mark Harrison**, UBC	Roundtable Discussion
3:30	***Refreshment Break: Posters, Exhibitors, and Networking (Theatre)*** ***BREAK SPONSORED BY MSFHR***		
4:00	*Targeting of Solid Tumors with Bi-Specific Antibodies and Bi-Specific drug Conjugates to Induce Novel Biologics and Drug-like Properties* **David Poon**, Zymeworks	*PROMs in Action: Changing Outpatient Asthma Care by Individualised Approach to Medication Adherence* **Mohsen Sadatsafavi**, Faulty of Medicine, UBC	
4:30	*Design, Synthesis and Evaluation of Novel Anabolic Bone Targeting Prodrugs for Treatment of Osteoporosis and Other Bone Conditions* **Bob Young**, Simon Fraser University	*Patient Reported Outcome Measures (PROMS): Do you Measure all that I Experience?* **Cheryl Koehn**, Arthritis Consumer Experts/JointHealth	
5:00-5:15	**Oral Presentation from Posters:** A First Report of an Intravesical Therapy with Activity in a Muscle Invasive Bladder Cancer Xenograft Model **Clement Mugabe**, CDRD	**Oral Presentation from Posters:** *How is Uncertainty in Risks and Benefits Presented in Patient Decision Support Interventions?* **Madelaine Bell,** UBC	
5:15-6:00	Posters, Exhibitors, and Networking (Theatre)		
6:30 PM	***Conference Gala and Awards Dinner (Fraser Room)*** ***6:30 Cash bar, 7:30 Dinner***		

FRIDAY, JUNE 3 - MORNING SESSIONS		
7:30 AM	Registration	
7:30 - 9:00	**SPONSORED BY AGILENT** **Breakfast Lecture:** **Adam Rosebrock, University of Toronto** ***Quantitative Mass-Spectrometry Metabolomics for Direct Biochemical Phenotyping*** *Chair:* Marcus Kim, Agilent	
9:00 - 12:00	**SESSION 10: Analytical Innovation to Support Precision Medicine and Biologicals Development** *Co-Chairs*: Christoph Borchers, University of Victoria, and David Kwok, BRI Biopharmaceutical Research Inc. ***(Whistler Ballroom A)***	**SESSION 11: Protein and Peptide Delivery** *Co-Chairs*: Brian Amsden, Queen's University, and Larry Unsworth, University of Alberta ***(Whistler Ballroom B)***
9:00	*Distinguishing Leucine and Isoleucine Residues in De novo sequencing of mAbs using Nano LCMSn: A Potential to Replace Edman Degradation* **Dhanashri Bagal,** Amgen	(9:00-9:10) **Trainee Presentation**: *Development of a Segmented Intravaginal Ring for the Combination Delivery of Hydroxychloroquine and siRNA-encapsulated Nanoparticles as a Novel Strategy for Preventing HIV Infection* **Yannick Traore,** University of Manitoba
9:30	*ImmunoMALDI MS as a Diagnostic Tool for Primary Aldosteronism* **Michael Chen,** Jewish General Hospital, McGill	*The Eyes Have It - Shifting Paradigms in the Delivery of Drugs to the Eye* **Heather Sheardown**, McMaster University *Hollow Metallic Microneedles for Intradermal Delivery* **Boris Stoeber,** UBC
10:00	***Refreshment and networking break***	
10:30	*Understanding Biotransformations of a Therapeutic mAb and the Impact on Clinical PK Assay Development* **Luna Liu**, Genentech	*New Strategies for Protein Delivery from Degradable Microspheres* **Brian Amsden**, Queen's University
11:00	*Multiplex and absolute protein quantitation by LC-MRM/MS for clinical research* **Christoph Borchers,** University of Victoria	*Bioinspired and Nanotechnology-enabled Delivery of Protein/Peptide Drugs for Diabetes and Diseases in the Brain* **Xiao Yu (Shirley) Wu,** University of Toronto
12:00	***Conference Concludes***	

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NANOMEDICINES BECOME PERSONAL: OPPORTUNITIES AND CHALLENGES

SESSION 11:

PROTEIN AND PEPTIDE DELIVERY

POSTER SESSION 1 - WEDNESDAY, JUNE 1
CSPS AND CC-CRS POSTERS

Biomedical Sciences

Clinical Sciences & Pharmacy Practice

Drug Delivery & Pharmaceutical Technology

Pharmaceutical & Analytical Chemistry

Speaker Abstracts

Tuesday, May 31

Industry Day:

Innovation and Management of Modern Pharmaceuticals

Plenary Lecture 1

SPONSORED BY: COLORCON

Chair: Amyn Sayani, GSK

New Trends in Pharma-Academia Collaborations for Drug Discovery

Carolyn A. Buser-Doepner, Vice President of Discovery Partnerships with Academia, GlaxoSmithKline

What are the challenges facing both pharmaceutical companies and academia in the discovery and development of novel medicines? How can we help each other to overcome these challenges? This presentation will describe different types of partnership models being pursued today and will demonstrate how pharma and academia can nicely complement one another. Specific examples will highlight the risks and benefits to these partnerships in our quest to benefit patients.

Carolyn Buser-Doepner
Carolyn A. Buser is Vice President of Discovery Partnerships with Academia at GlaxoSmithKline. She received her B.A./B.A. in chemistry and German from Bryn Mawr College, spent one year as a Fulbright Scholar at the Technical University of Braunschweig in Germany, and obtained her Ph.D. in Biophysical Chemistry at Yale University in 1992. She was a Damon Runyon – Walter Winchell postdoctoral fellow at the State University of NY at Stony Brook and subsequently served as Research Assistant Professor. In 1996, Carolyn joined the Oncology group at Merck Research Labs, holding positions as preclinical team leader for several drug discovery programs, director of Oncology Health Care Solutions, and finally senior director of External Scientific Affairs in Oncology. In March 2011, Carolyn joined GlaxoSmithKline (GSK), where she now leads a team of drug development scientists who identify and progress novel targets in partnership with biology and disease experts in academia. Within GSK, she co-chairs a global Biology Council and the GSK Fellowship program and is a member of the Technology Investment Board and Discovery Investment Board. Carolyn is a member of AACR, AAAS, and ASCO and is bilingual in German.

Showcasing Drug Discovery Companies

Chair: Jason Crawford, CDRD

Human Channelopathies: Providing Key Insights into Drug Development

Robin Sherrington, PhD, Senior Vice President, Business & Corporate Development, Xenon Pharmaceuticals Inc.

Drug development remains a high-risk, high-cost and time-consuming endeavour. Selecting good drug targets for medications is one key to potentially lowering risk and cost of development.

PCSK9 inhibitors provide the most recent example of how human genetics has elucidated an exquisite mechanism for drug targeting to great effect. An area of future opportunity exists in voltage gated sodium channels. Numerous sodium channel modulators which are used across multiple disease states, including pain, epilepsy and cardiac arrhythmias are commercially available. While these drugs have significant potential for efficacy, they are limited by the potential for adverse events given their lack of target selectivity.

Knowledge of a new voltage gated sodium channel binding site has enabled the discovery of differentiated and more selective ion channel modulators and genetics is allowing the elucidation of key voltage gated sodium channels to target selectively.

The presentation will discuss select human channelopaties and the targets underlying them as potential new drug targets.

Robin Sherrington

Dr. Sherrington has served as the Senior Vice President, Business & Corporate Development, at Xenon Pharmaceuticals Inc. since February 2012, and as Xenon's Vice President, Business & Corporate Development, from January 2010 to February 2012. He has held various Senior Director positions in business development and other departments since joining Xenon in March 2001.

Prior to joining Xenon, Dr. Sherrington worked at Pfizer, Inc., a global pharmaceutical company, as a neuroscientist from 1999 to 2001. Dr. Sherrington also served as Director of Neuroscience from 1996 to 1999 at the biotechnology companies Axys Pharmaceuticals and Sequana Therapeutics. Prior to 1996 Dr. Sherrington was a post-doctoral fellow at the University of Toronto. He received his Ph.D. from the University College London and his B.Sc. with honors from the University of Reading.

Alectos Therapeutics: Targeted Innovation in Preclinical Drug Discovery

Ernest McEachern, PhD, President & CEO, Alectos Therapeutics

Alectos Therapeutics is a privately held pharmaceutical company dedicated to the discovery and development of novel small-molecule therapeutics for the treatment of human disease. We focus on preclinical drug development, target validation, hit-to-lead optimization, and IND-enabling studies. Alectos develops innovative new strategies to address medical conditions for which there are no effective treatments. At Alectos, we work together with academic scientists to investigate and validate fundamental science around new drug targets, and we establish early partnerships with pharma to advance our programs into the clinic. Our long term vision is to build a sustainable company to commercialize discoveries from the Canadian life sciences community.

Alectos began operations as a spin-off from basic research conducted at Simon Fraser University into the relationship between the O-GlcNAcase (OGA) enzyme and Alzheimer's disease. This work led to a license and research collaboration between Alectos and Merck & Co., Inc. valued at over $289M. Today, our most advanced program is directed toward developing the first-in-class OGA inhibitor MK-8719 for treatment of Progressive Supranuclear Palsy (PSP), Alzheimer's disease, and other related neurodegenerative disorders. This program was recently granted Orphan Drug Status by the US FDA. As part of its pipeline, Alectos is also actively advancing discovery-stage programs in oncology and neurology, including development of small-molecule glucocerebrosidase (GBA) activators for Parkinson's disease.

Ernest McEachern

Dr. McEachern received his PhD from UBC and

carried out postdoctoral studies at Stanford University. Dr. McEachern has over seventeen years' experience in scientific and leadership roles in the pharmaceutical industry. He served in various capacities at AnorMED Inc. including leading a discovery team that developed the HIV entry inhibitor AMD070. Dr. McEachern is a co-founder of Alectos Therapeutics and directed the scientific and business development activities that led to the $289M license and research collaboration agreement between Alectos and Merck & Co., Inc. He is President and CEO of Alectos Therapeutics and serves on the Board of Directors. Dr. McEachern is co-author on over 60 publications and patents.

Novel Delivery Technologies for Therapeutics

Chair: Pieter Cullis, UBC

Zymelink™ - Next Generation Drug Conjugates

John Babcook, Senior VP, Discovery Research, Zymeworks Inc.

The Zymelink™ drug conjugation platform is modular suite of site-specific conjugation technologies, customizable linkers, and proprietary cytotoxic payloads designed for the targeted delivery of therapeutics with optimal efficacy and safety profiles. The Zymelink™ conjugation platform is compatible with traditional monoclonal antibodies and with the Azymetric™ (bi-specific) and AlbuCORE™ (multi-specific) platforms for the development of next-generation biotherapeutics.
Zymeworks Inc. www.zymeworks.com
Zymeworks is a privately held biotherapeutics company that is developing best-in-class Azymetric™ bi-specific antibodies and antibody drug conjugates for the treatment of cancer, autoimmune and inflammatory diseases. The company's novel Azymetric™, AlbuCORE™, and EFECT™ platforms, its Zymelink™ conjugation platform and cytotoxins, and its proprietary ZymeCAD™ structure-guided protein engineering technology, enable the development of highly potent bi-specific antibodies, multivalent protein therapeutics, and antibody drug conjugates across a range of indications. Zymeworks is focused on accelerating its preclinical biotherapeutics pipeline through in-house research and development programs and strategic collaborations.

John Babcook
John Babcook is Zymeworks' Senior Vice President Discovery Research responsible for target, antibody, and drug conjugate discovery and associated partnerships. For over 20 years, Mr. Babcook has made significant contributions to the international biotechnology industry. Based on a novel antibody generation platform, he co-founded ImmGenics Pharmaceuticals which was acquired by Abgenix and subsequently by Amgen, where he led its Canadian research team. Mr. Babcook also established the Biologics Division at the Centre for Drug Research and Development (CDRD) where served as VP Biologics in addition to becoming the founding President and Chief Scientific Officer of Kairos Therapeutics. While at Kairos, he was responsible for the development of its ADC therapeutics pipeline and formed multiple collaborations, including the strategic partnership and the merger with Zymeworks. Mr. Babcook has participated in the development of more than 100 therapeutic antibody-based programs, 11 of which are now in the clinic, including three antibody-drug conjugates.

Mr. Babcook is an Adjunct Professor in Molecular Biology and Biochemistry at Simon Fraser University, an Honorary Doctorate recipient from the British Columbia Institute of Technology and the recipient of the LifeSciences British Columbia's "Innovation and Achievement" Award.

The NanoAssemblr Platform: Microfluidic-based Manufacture of Nanomedicines from uLs to 10sL

James Taylor, CEO and Co-Founder, Precision NanoSystems, Inc.

Conventional methods for producing nanomedicines pose numerous challenges. These include being labour intensive, difficult to reproduce, difficult to scale, and limited in the compositional scope of the nanoparticles produced. The NanoAssemblr™ platform provides an automated microfluidics-based technology for the easy, reproducible, and scalable manufacture of nanomedicines. Here, we will describe the microfluidic platform and its application in the development of a variety of nanoparticle compositions, including liposomes, LNP-RNA, polymer, and others. We describe strategies to tune the physical attributes of the nanoparticles, including size, encapsulate API at high efficiencies, and seamless scale manufacturing volumes from µL to 10s L.

James Taylor
James Taylor is the CEO and co-founder of Precision NanoSystems, Inc. (PNI), a manufacturer of instruments, kits and reagents in the global nanomedicine market providing tools for drug development and cell-specific delivery to study, diagnose and treat disease. PNI's flagship product, the NanoAssemblr™ Benchtop instrument, allows scientists to rapidly develop novel nanomedicine drug candidates for pre-clinical testing. PNI's NanoAssemblr Scale-up platform enables the translation of these drug candidates to clinical testing and eventually to commercial use. PNI sells its products to leading pharmaceutical and biotechnology companies, and leading academic institutions in over 20 countries worldwide. Please find more information at http://www.precisionnanosystems.com/. James has a B.A.Sc. in engineering physics from UBC and a Ph.D. in genetics from the Institute for Systems Biology in Seattle, WA.

A Lipid Nanoparticle Platform to Enable mRNA Therapeutics

Michael Hope, Chief Scientific Officer, Acuitas Therapeutics

Previously we developed a class of lipid nanoparticles (LNPs) suitable for systemic delivery of siRNA drugs that successfully transitioned from research into the clinic for hepatic gene silencing applications, including a product (Patisiran) for the treatment of transthyretin amyloidosis (Alnylam/Genzyme to file NDA in 2017). We are now applying this clinically proven LNP delivery platform to enable the emerging field of mRNA-based therapeutics. LNPs encapsulating mRNA have many exciting clinical applications including transient expression of hepatic proteins to manage diseases; permanent hepatic gene editing (both gene deletions and insertions) to cure diseases; using the liver as a bioreactor to excrete proteins such as antibodies and to deliver mRNAs expressing antigens for the rapid development of new vaccines. We will describe the platform and present *in vivo* data demonstrating the potential for a broad range of mRNA-LNP therapeutics.

Michael Hope
Dr. Hope obtained his Ph.D. in Membrane Biochemistry from the University of London, U.K. He has held senior academic and industry positions including Assistant Professor the Department of Medicine, University of British Columbia, co-founder and Vice President Research at the Canadian Liposome Company and co-founder and Principle Scientist at Tekmira Pharmaceuticals. In 2009 he co-founded Acuitas Therapeutics and is Chief Scientific Officer. He has worked in the field of lipid nanoparticle drug delivery for 40 years, including the delivery of nucleic acid therapeutics, with over 100 publications in peer reviewed journals.

Pharma at the Forefront in Drug Discovery

Chair: Robert Young, SFU

Translational Biology in the IO Space - Patient Response, Combination Therapies, New Approaches

Jennifer Yearley, Senior Principal Scientist and Director, Anatomic Pathology Group, Merck's Biologics Discovery, Palo Alto, CA

Despite the unprecedented successes of novel immune-based therapies that have exploded onto the scene for treatment of cancer in recent years, not all patients respond, some responses are delayed, these delays can sometimes be very prolonged, and the magnitude of response is variable. Our understanding of the drivers behind these differentials is still poor. Furthermore, as attention shifts from monotherapies to combination therapeutic approaches to try to increase efficacy and to expand the patient populations who are helped by these approaches, there arises a burning need for tools which will help us devise rational combination testing strategies. There is a near infinite number of possible combination approaches, many more than can reasonably be tested even in preclinical contexts, and with addition of multiple interventions, there is further increased complexity in response prediction for potential patient selection. Strategies to address these concerns need to be based on development of deep understanding of the biology being targeted and changes induced by treatment. Approaches being taken at Merck to address these issues will be discussed.

Jennifer Yearley
Jennifer is Senior Principal Scientist and director of the Anatomic Pathology group at Merck's Biologics Discovery site in Palo Alto, California. She oversees the group's functions as a center of excellence for development of intact tissue based assays, supporting protein-based molecular epidemiology studies in human tumor specimens as well as larger scale predictive biomarker development in the immuno-oncology space. Dr. Yearley co-leads Merck's efforts to enhance collaborative translational research undertakings efforts in human tumor immunology with external academic investigators.

Prior to coming to Merck, Dr. Yearley worked in Drug Safety Evaluation at Bristol-Myers Squibb. She did her pathology residency at Harvard Medical School, her PhD in models of HIV pathogenesis at the University of Massachusetts Graduate School of Biomedical Sciences, and a DVM at Washington State University.

Psoriasis - From Transformational Treatments to Cure and Prevention

Anne Fourie, PhD, Senior Director, Psoriasis Disease Area Stronghold Leader, Janssen Research & Development

[Abstract not available]

Anne Fourie
Anne is the Disease Area Stronghold leader for Psoriasis within the Immunology therapeutic area at Janssen Research & Development, LLC, a pharmaceutical company of Johnson & Johnson. In this role, she has responsibility for scientific strategy and therapeutic portfolio in Psoriasis Research and Development. Since joining Janssen 20 years ago, she has held leadership roles of increasing responsibility within Drug Discovery, and served on several Development teams for early stage therapeutics. Anne obtained her PhD in Biochemistry at the University of Cape Town, South Africa, and completed a post-doctoral fellowship at UT Southwestern Medical Center in Dallas.

New Commercialization Strategies, Regulatory Challenges, Big Data Issues

Chair: Jason Crawford, CDRD

New Commercialization Strategies

David J. Main, President & CEO, Aquinox Pharmaceuticals Inc., Vancouver, BC

Over the last decade multinational pharmaceutical companies have suffered numerous patent expiries and declining R&D productivity. David will review these trends and highlight his experience from the past 25 years demonstrating that the biotechnology industry has become the engine for innovation in pharmaceutical research. Similarly, David will review trends in the investment sector that have spawned a new generation of independent pharmaceutical companies such as: Biogen-Idec, Celgene, and Gilead.

David J. Main
Mr. Main has over 25 years experience in the pharmaceutical industry and brings a demonstrated ability to grow and finance pharmaceutical development companies. As a co-founder of Aquinox, Mr. Main has overseen the advancement of the Company's lead product, AQX-1125, from a target validation program to now entering Phase 3 studies. During this time he has also been responsible for the transition of Aquinox from a private to a NASDAQ-listed public company with over US$200 million raised to date in equity capital. Mr. Main was formerly the President and CEO of INEX Pharmaceuticals Corp. and, prior to INEX, was Vice President at QLT Inc., one of Canada's inaugural biotech companies. Mr. Main began his career as a licensed pharmacist at the Royal Columbian Hospital in New Westminster, B.C. He holds a B.Sc. (Pharmacy) and an MBA from the University of British Columbia (UBC). Mr. Main formerly served as the Chair of LifeSciences BC (formerly BC Biotech), is currently the Chair of BIOTECanada and a Director of BIO.org as well he also serves on a number of private and not-for-profit Boards.

Access to New Medicines, Do Canadians Deserve Better?

Farzad Ali, Director of Access for Oncology, Vaccines and Innovative Products, Pfizer Canada

In the last decade, the nature of pharmaceutical drug discovery and areas of research have evolved. The pharmaceutical research sector is targeting areas of unmet need and difficult to treat illnesses while aiming for clear differentiation between new medicines and the current treatments.
Meanwhile, we have seen drastic changes in pharmaceutical policy with the ultimate goal of using public funds appropriately, investing only in medicines that provide value and ensuring the sustainability of public drug plans.

But have we gone too far with respect to the access hurdles we have put in place in the Canadian system for a new medicine? Have we created too stringent a labyrinth pathway for access? How do we compare to other countries and what could be the possible solutions to make things better?

The goal of this talk would be to fuel debate and discussion on how to make the access pathway in Canada more efficient while still respecting the tenets of sustainability and paying for value.

Farzad Ali
Farzad is a pharmacist and a health economist. He joined Pfizer in 2000 as an Outcomes Research Manager. In this role, he led economic evaluations and put in place disease management initiatives in the area of hypertension and anti-infectives.

In early 2009, Farzad was appointed the Director of the Heath Economics & Outcomes Research department where he led a team of health economists and epidemiologists assessing the cost-effectiveness of Pfizer's portfolio of medicines including oncology, while ensuring evidence dossiers are built to better meet the needs of the payers and health technology assessment (HTA) bodies.

Farzad has published on several health technology assessment (HTA) related topics. He is a long standing member of the International Society of

Pharmaco-economics and Outcomes Research (ISPOR) as well as the Health Technology Assessment international (HTAi).

Farzad was appointed in 2009 to the Ontario Ministry of Health's Drug Innovation Fund review panel. He sits on the Canadian Agency for Drug and Technologies in Health (CADTH) Scientific Working Group and is on the Conference Board of Canada's Advisory Committee for Sustainable Healthcare.

He is currently the Director of Access for Oncology, Vaccines and Innovative products for Pfizer Canada.

Privacy, Governance & Innovation in the Era of Big Data

Paul Terry, CEO & CTO, PHEMI Systems, Vancouver, BC

Big Data has been used extensively by the likes of Google, Netflix, and Facebook for over 10 years and has proven that it can provide companies with the ability to innovate and rapidly respond to changing business, scientific, and research environments. Able to economically scale to handle vast and varied datasets for data mining and insight, the challenge for big data in industries that hold sensitive data, such as the life sciences and pharmaceutical sectors, is how to effectively balance the responsibility of protecting privacy with the need to innovate. Learn how organizations are addressing the real challenges of privacy, security and governance in such a way they can effectively mine all of their data, while also protecting the privacy of individuals.

Paul Terry

Paul provides the vision and technical leadership at PHEMI, combining his visionary approach to technology and ability to bring new technologies to reality, with 30 years of experience in healthcare, high performance computing, and telecommunications. He now leads PHEMI in enabling enterprises in and beyond the healthcare industry to capitalize on their data and become data-driven innovators.

He currently serves on the Board of Directors for Providence Health Care, Genome BC, Life Sciences BC, and Molecular You, and is an advisor to the BC provincial government on next-generation data strategies. He is an adjunct professor in big data at Simon Fraser University and is a partner with Magellan Angel Partners. Paul is a sought-after speaker on data strategy, and privacy initiatives. He is a member of the BC Institute for Health Innovation and the Genome BC's Health Strategy Task Force, and has co-founded several of Canada's most successful technology start-ups.

Tuesday, May 31

Plenary Lecture 2

Chair: Catherine Lau, Janssen Inc.

Are Innovative Medicines and our Life Sciences Industry at Risk in Canada?

Chris Halyk, President, Janssen Inc. (Pharmaceutical Companies of Johnson & Johnson)

"There are still many diseases for which there is no cure, and effective medicines must be found. Although we have contributed to the solutions for some of these problems, we will continue our research efforts, because so much more needs to be done." The quote, from our founder, Dr. Paul Janssen, one of the most prolific researchers and innovative medicines developers in the past 50 years continues to ring true today in 2016. Although we have made great progress and are transforming what were once acute and deadly illnesses (HIV, HEP C, cancer) into chronic illnesses or cures there is no resting among discovery scientists, clinical researchers, or at Janssen. Patients' lives depend on it.

The environment we face today related to innovative medicines is a challenging one with significant layers of bureaucracy between discovery and access for patients to these much needed treatments. Multiple layers of government review and adjudication including regulatory, health technology assessment and price and value evaluations are hard-wired into our Canadian system resulting in significant access delays for patients. As these hurdles continue to rise our ability to attract global life sciences investment to Canada is under extreme pressure. Although we understand these barriers and are doing our best to overcome them we also know that what we are doing today needs to change in order to meet the evolving challenges of health care system sustainability in the future.

Today payers pay for medicines – tomorrow they may be reimbursing for patient outcomes. Together, we must be on the leading edge of improving the way innovative medicines are brought to the health care system and patients. Leveraging real world evidence; leading in the changing world of research and development that no longer looks like it did 20 years ago or even 5 years ago; focusing on optimal outcomes for patients and for the health care system; these are the future directions we must lead and create. Public/private partnerships with the goal of delivering better health care for populations is the future and let's ensure together we will continue to grow our already demonstrated leadership on this front.

Chris Halyk

Chris Halyk was appointed President, Janssen Inc. in early 2006. Janssen is a brand name pharmaceutical company headquartered in Toronto, Canada and part of the Johnson & Johnson Family of Companies.

Mr. Halyk began his career with Johnson & Johnson when he joined Janssen Pharmaceutica Inc. in 1986 as an Over the Counter (OTC) product manager. Since then, Mr. Halyk held a number of sales and marketing roles of increasing responsibility including district sales manager, national sales director and, with the merger of Janssen Pharmaceutica and Ortho-McNeil in 1995, group product director, Gastrointestinal/Infectious Disease (GI/ID).

In 1997, Mr. Halyk was appointed Vice-President, Sales and Marketing and a member of the Janssen Management Board. His responsibilities included innovations in direct-to-consumer advertising, patient education programs and sales force automation.

In 2001, Mr. Halyk was appointed Managing Director of Ortho Biotech, the biopharmaceutical division of Janssen Inc.

Before joining the company, Mr. Halyk worked for Warner-Lambert, a pharmaceutical company in Toronto.

Born and raised in Canada, Mr. Halyk holds an Honours Business Administration degree from the University of Western Ontario. He served as the Chair of the Board of Directors for Rx&D, the industry association for Canada's Research-Based Pharmaceutical Companies from 2012 until 2013. He is married, has three children and lives in Oakville, Ontario.

Wednesday, June 1

Plenary Lecture 3

Chair: Corey Nislow, UBC

New Therapeutic Strategies to Target the Mitochondria in Leukemia

Aaron D. Schimmer, MD, PhD, FRCPC, Princess Margaret Cancer Centre, Ontario Cancer Institute, University of Toronto, Toronto, Canada

Our understanding of the molecular mutations associated with acute myeloid leukemia (AML) has improved, but most of these mutations are not directly "drugable". Thus, new therapeutic approaches for AML may need to target pathways and biological vulnerabilities downstream of these genetic mutations. My laboratory is focused on developing novel therapeutic strategies for AML by identifying and targeting unique biological vulnerabilities in their mitochondria.

We recently demonstrated that AML cells and stem cells have dysregulated mitochondrial characteristics. Compared to normal hematopoietic stem cells, AML cells and AML stem cells have increased mitochondrial biogenesis, increased mitochondrial mass, and a greater dependence on oxidative phosphorylation

For example, using genetic and chemical approaches, we demonstrated that AML cells and stem cells are uniquely sensitive to inhibition of mitochondrial protein translation. As a chemical approach, we inhibited mitochondrial protein translation with the antimicrobial tigecycline. We showed that tigecycline inhibited mitochondrial protein translation, repressed oxidative phosphorylation, and killed AML cells and stem cells in vitro and in vivo.

The robust preclinical anti-leukemia activity of tigecycline and its known toxicology and pharmacology in humans and animals, allowed us to rapidly advance this drug into clinical trial for leukemia to assess the biological and clinical effects of inhibiting mitochondrial protein synthesis in AML. We recently completed a multi-center phase I trial of escalating doses of tigecycline in patients with relapsed and refractory AML.

We also recently identified new "drugable" targets in the mitochondria of AML cells including the mitochondrial protease ClpP.

In this presentation will we highlight new biological vulnerabilities in AML, describe potential new therapeutic targets, and discuss our efforts to bring new therapies into clinical trial for this disease.

Aaron Schimmer

Dr. Schimmer is a Staff Physician and Senior Scientist at the Princess Margaret Cancer Centre, University Health Network and Ontario Cancer Institute. He is the current head of the leukemia program at the Princess Margaret and a member of the executive of the Ontario Cancer Institute. Dr. Schimmer holds the Baker Chair in Leukemia and Related Diseases at the University Health Network. Dr. Schimmer is a Professor in the departments of Medicine and Medical Biophysics at the University of Toronto. He is also the President of the Canadian Hematology Society.

Dr. Schimmer graduated from medical school at the University of Toronto and completed specialty and subspecialty training in internal medicine in and hematology. He subsequently pursued research training and received his PhD in Molecular Biology in 2001. Dr. Schimmer then undertook a post-doctoral fellowship at the Burnham Institute in San Diego, California prior to his return to the Princess Margaret.

The Schimmer lab is focused in on developing new therapeutic strategies for leukemia with an interest in targeting unique biological vulnerabilities in AML and AML stem cells. He has advanced 3 drugs into clinical trial from his lab and has been the Principal Investigator on 9 additional clinical trials of novel agents for leukemia. Dr. Schimmer is the author of over 180 publications and is an inventor on over 20 patent applications. He has received over 35 awards and honours for academic achievement including Scholar in Clinical Research by the Leukemia and Lymphoma Society, and the Bernard and Francine Dorval young investigator award from the Canadian Cancer Society.

Wednesday, June 1

SESSION 1:

Special Populations

Chair: Abby Collier, UBC

Pediatric Development of Metabolizing Enzymes

Abby Collier, Associate Professor of Pharmacology, Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver

This presentation focuses on the physiology, maturational processes and timelines in the developing fetus, neonate and infant as critical parameters in the disposition of xeno- and endobiotics. Emphasis will be on hepatic development as the key mediator of drug and chemical disposition. Developmental pharmacology of the major metabolizing enzyme families Cytochromes P450 (CYP), UDP-glucuronosyl-transferases (UGTs), and Sulfotransferases (SULTs) vary with some enzymes higher in fetal life (some P450s and Sulfotransferases) and others developing in the neonatal or childhood period (UGTs, some P450s). The influence of transporters and their impacts on xeno- end endobiotic disposition in concert with metabolism will also be discussed. These biochemical aspects of pediatric sensitivity are coupled with neonatal and pediatric physiological changes including differences in: serum proteins, microsomal and cytosolic protein per gram of liver (MPPGL) and changes in liver volumes and blood flows that occur differentially and mature during late childhood or adolescence. Lamotrigine and morphine will be used as examples of exposures where neonatal and pediatric toxicity is higher due to differential biochemical development of UGT enzymes, as well as physiological maturation. Acetaminophen toxicity in neonates and infants will be used to illustrate how toxicity can depend on dose and overlapping enzyme specificity, with differential capacity between SULTs and UGTs. The ascendance of physiologically-based pharmacokinetic modeling for prediction of drug and chemical disposition in the pediatric population will be introduced including a discussion of parameters that are known and those the field currently lacks but needs.

Abby Collier
Originally from New Zealand, Dr. Collier received her BSc in pharmacology from the University of Auckland in 1998 and her PhD in pharmacology from the same institution in 2003. After a postdoctoral fellowship with Professor Chris Pritsos at the University of Nevada, Dr. Collier was an assistant professor, then associate professor at the University of Hawaii Medical School from 2006 to 2013. A member of the Faculty of Pharmaceutical Sciences at UBC since 2013, Dr. Collier teaches pharmacology to undergraduate, graduate, pharmacy and medical students and maintains an active and well-funded research lab. Dr. Collier's sub-specialty is drug metabolism and pharmacokinetics, primarily the phase II (conjugation) enzymes, with a strong focus on pregnancy and pediatrics. A winner of the 2011 SimCYP Consortium Award for Most Informative Report ("in recognition of scientific research that is leading the field in ADME, IVIVE, pharmacokinetics, modeling and simulation"), Dr. Collier uses a combination of wet laboratory work and in silico modeling to provide greater understanding of developmental pharmacology and improve drug/chemical safety. Along with her collaborators, she also performs research and publishes regularly in the fields of human and environmental toxicology and endocrinology.

PBPK Modelling and Simulation in Pediatric Drug Development

Andrea N. Edginton, School of Pharmacy, University of Waterloo, Waterloo, ON, Canada

Physiologically based pharmacokinetic (PBPK) modeling and simulation in drug development has gained traction, especially in the areas of drug-drug interaction (DDI) prediction and pediatrics. Pediatric pharmacokinetic, safety and/or efficacy studies are

mandatory during the drug development process in North America and Europe. The promise of biologically-based extrapolation to derive the first-in-children dose has been a driving force in the use of PBPK models in the design of pediatric clinical trials and they are recognized by regulators as a potentially useful tool to this end.

The workflow for PBPK model development of virtual pediatric populations depends on the stage of drug development and the available pre-clinical and clinical data (e.g. candidate vs. marketed drug product). Model simulation outcomes, such as exposure as a function of age or weight, are used to plan clinical trials (e.g. doses, sampling times, sample size). Examples of PBPK model use in planning pediatric clinical trials will be presented including defining dose and simulating DDI potential as a function of age. Model outcomes are greatly dependent on the information that is used to parameterize the model. This information is categorized as drug specific (e.g. affinity of drug for enzyme) or organism specific (e.g. amount of enzyme per gram of liver). Ongoing research on closing organism-specific knowledge gaps that will improve our confidence in model outputs will be discussed such as the age dependence of gastrointestinal solubility and small intestinal transit time for appropriate parameterization of a pediatric gastrointestinal tract model. Quantifying pediatric-specific parameters is an important area of future research.

Andrea N. Edginton

Dr. Edginton is an Associate Professor and Program Assessment Officer at the School of Pharmacy at the University of Waterloo in Ontario, Canada, is the Chair of the University's Clinical Research Ethics Board and has a PBPK consulting company called Design2Code Inc. Before coming to the University, she worked in the Systems Biology group at Bayer Technology Services in Leverkusen, Germany. As an academic, Dr. Edginton's research focuses on the development and application of physiologically-based pharmacokinetic (PBPK) models and simulation techniques in both the areas of pharmaceuticals and human health risk assessment. Her research examines how the physiology of sub-populations such as children and patients with disease (e.g. obesity, liver cirrhosis) affect the pharmacokinetics of drugs and how this information can be integrated into PBPK models for the optimization of drug therapy. Of special interest is the physiological scaling of PBPK models from adults to children as a means to predict drug pharmacokinetics and quantify appropriate dosing regimens for clinical trials in children.

Developmental Pharmacology – ADME Consequences in Children

Catherijne A.J. Knibbe, Leiden Academic Centre for Drug Research, University of Leiden, Leiden, & Department of Clinical Pharmacy, St Antonius Hospital Nieuwegein and Utrecht, The Netherlands

In children, the majority of drugs is still used in an empirical manner. For children, around 37% of drugs used in community practice and 80% of drugs used in neonatal intensive care are prescribed in an off-label or unlicensed manner. To define the optimal dose for each individual child, differences in the pharmacokinetics (PK) and preferably also the pharmacodynamics (PD) should be considered.

In the lecture, results of clinical and PK data analysis studies are presented in which on the basis of advanced population modelling doses for specific drugs can be adjusted. After proper internal and external validation of these models, subsequent prospective clinical trials are designed in which the novel dosing guidelines are evaluated upon which the guidelines in formularies are to be updated.

While this approach has already proven successful for the substantial number of drugs, it requires a tremendous amount of resources and time to thoroughly investigate changes in PK parameters of each individual drug for each age group, and approaches to expedite the development of adjusted dosing regimens are also needed. From proof-of-principle studies that will be presented, it can be concluded that validated covariate models for children, derived on the basis of comprehensive covariate analyses, may also contain biological system specific information that can be used for extrapolation to drugs that share the same elimination pathway, provided specific drug properties are taken into account. As such, an approach is generated that can be considered a semi-physiological hybrid between empirical population modelling and physiologically-based pharmacokinetic modelling that may accelerate individualized drug dosing for each individual with a certain age and weight in an efficient manner.

Catherijne Knibbe

Catherijne Knibbe is Professor of Individualized

Drug Treatment at the Division of Pharmacology at Leiden University, the Netherlands, staff hospital pharmacist-clinical pharmacologist in the St. Antonius Hospital Nieuwegein, and research worker at the Department of Paediatric Intensive Care, Erasmus MC/Sophia Children's Hospital Rotterdam, the Netherlands.

Supported by a Veni (2006) and a Vidi (2013) grant from the Dutch Organization of Scientific Research NOW, she combines her clinical responsibilities as a hospital pharmacist-clinical pharmacologist in Anesthesiology and Intensive Care with a research group developing rational dosing schemes for paediatric indications using population PK-PD modeling within a multidisciplinary and multicentre platform. More recently, she has extended her research line to develop individualized dosing schemes for morbidly obese children and adults (BMI>40 kg .m-2), for which a large number of clinical trials have been initiated.

She has supervised 12 PhD theses, is currently supervising 10 PhD students and 2 Postdocs, and has co-authored more than 120 international peer-reviewed publications and book chapters. Knibbe is supervisor of the clinical pharmacology training program, co-supervisor of the hospital pharmacy training program, vice-chair of the Central Committee of Research Involving Human Subjects (the 'CCMO'), chair of the national Concilium Hospital Pharmacy, board member of the Dutch Society of Clinical Pharmacology and Biopharmacy, and member of the Committee Priority Medicines for Children/Elderly (ZonMw).

Wednesday, June 1

SESSION 2:

Regulatory Challenges and Opportunities

SPONSORED BY: SANDOZ CANADA

Chair: Fakhreddin Jamali, University of Alberta

Regulatory Issues on the Determination of Bioequivalence for Modified-Release Formulations with Multiphasic Concentration Profiles

Laszlo Endrenyi, University of Toronto, ON

The most usual regulatory expectation for the determination of bioequivalence (BE) is that the 90% confidence interval around the ratio of geometric means of primary parameters (AUC and C_{max}) of two drug products should be between 0.80 and 1.25. However, the approach does not always indicate the therapeutic equivalence of the formulations. For example, with some modified-release (MR) formulations having complicated concentration profiles, it is not sufficient to satisfy the BE expectations only for the primary parameters. FDA and EMA recommended BE requirements for an additional parameter, the partial AUC (pAUC). However, it is not clear how the cut-off time limiting pAUC should be set. FDA expects clearly defined time-points whereas EMA suggests that the cut-offs be evaluated on a case-by-case basis. FDA established science-based cut-offs, for instance, for MR zolpidem and methylphenidate (MPH). The latter were more recently empirically tightened. Generic MR-MPH formulations have very differing concentration profiles each of which is bioequivalent with that of the reference product. Consequently, the case-by-case approach of regulation may have merit. Furthermore, interchangeability among the diverse generic products could be questioned.

Laszlo Endrenyi

Laszlo Endrenyi is Professor Emeritus of pharmacology and biostatistics in the University of Toronto. He has served the university in various positions including on its Governing Council and as Associate Dean of Graduate Studies. He sat on the Board of Directors of the American Statistical Association and the Canadian Society for Pharmaceutical Scientists; he was a president of the latter. Externally, he has served on grant review committees and editorial boards of research journals including the Amer. J. Physiol, J. Pharmacokin. Pharmacodyn., J. Pharm. Pharmaceut. Sci., Biosimilars, and J. Pharm. Sci. He has received several recognitions, including an honorary doctorate from the Semmelweis University of Medicine. He is a Fellow of the Canadian Society for Pharmaceutical Sciences and of the American Association of Pharmaceutical Scientists and received the Lifetime Achievement Award of the latter.

Dr. Endrenyi published a book on Kinetic Data Analysis and over 190 research papers. Several of these established principles for the design and analysis of enzyme and pharmacokinetic investigations. These included principles and applications of optimal study designs. More recently, he extensively developed principles and applications for the evaluation of bioavailability, bioequivalence and biosimilarity. He developed various sensitive measures characterizing the rate of drug absorption. He extensively investigated issues of drug interchangeability.

Dr. Endrenyi's studies were instrumental in the adoption of some regulations and the withdrawals of others. He has consulted with the Food and Drug Administration and Health Canada and served on their advisory committees. He has consulted also with industry in the areas of pharmacokinetics, biostatistics, the design and evaluation of experiments, clinical trials, and the analysis of bioavailability, bioequivalence and biosimilarity studies.

Current Status of Decision-making for Biosimilars in Canada

Agnes V. Klein, MD, DPH, Director, Centre for the Evaluation of Radiopahrmaceuticals and Biotherapeutic Products, Biologics and Genetic Therapies Directorate, Health Canada

This presentation will provide an insight on how decisions are taken in respect of biosimilars in Canada and the reasons for those decisions.

Health Canada (HC) is also in process of bringing the Framework Guideline up to date in consideration of the experience to-date, its decision-making authority and comments received from stakeholders following the posting of the previous update posted for that purpose.

We are confident that, while the approach to biosimilars in Canada was and continues to be very similar to that in other jurisdictions, the next version of the HC Guidance will also demonstrate those similarities, thus bringing the document up to date and in line with current international thinking and advances in the area of biosimilars.

Agnes V. Klein

Agnes V. Klein, MD, DPH, is currently the Director, Centre for the Evaluation of Radiopahrmaceuticals and Biotherapeutic Products in the Biologics and Genetic Therapies Directorate.

After receiving her medical degree from the University of Toronto, Dr. Klein trained in Endocrinology, Medical Biochemistry and Public and Community Health. After joining Health Canada, she has occupied many and varied positions, scientific and managerial. Amongst relevant accomplishments, she represented Health Canada on NCBHR, as founding member and NCEHR as well as chairing the Committee on Clinical Trials of the Council.

In 2000, Dr. Klein moved to Biologics where she actively participated in the inception of the new Directorate and its processes.

Dr. Klein was an active participant in the CIOMS document on Pharmacogenetics and Pharmacoeconomics as well as in the ICH process drafting of guidelines (ICH E15 and E16 on pharmacogenomics). In addition to her special interest in biomarkers, surrogate endpoints and the appropriate design of clinical trials, especially the issues related to small studies, she is also interested in the regulatory and clinical issues regarding subsequent entry biologics (SEBs). This interest has included authorship and co-authorship of several articles on biosimilars.

Dr. Klein has made numerous presentations to professional and regulatory groups on issues surrounding the ethics of clinical trials and the integrity of clinical trial data, and has also presented on a wide-variety of new regulatory endeavours, including biosimilars.

Dr. Klein has also been involved actively with the various meetings organized through the Drug Information Association.

Dr. Klein is an active supporter for excellence in the development of medicines. As such she has been closely involved in the drafting of guidelines for the development and review of Orphan Drugs as well as biosimilars.

Challenges in Ensuring Drug Product Quality in the Product Lifecycle

Krishnan Tirunellai, Ph.D., Senior Scientific Advisor, Bureau of Pharmaceutical Sciences, Therapeutic Products Directorate, Health Canada

Of the three essential elements of a drug product: Safety, Efficacy and Quality, only Quality can be verified in each lot. Hence, it is a realistic indicator for managing product lifecycle. A product lifecycle has many important milestones such as changes in drug substance and drug product source, manufacturing process, stability etc. Outsourcing of material has introduced new variables that are often unpredictable. If the sponsor has a reliable Pharmaceutical Quality System and a good understanding of products, the product lifecycle could be managed more predictably to ensure a constant supply of good quality products to Canadians. The talk will address ongoing challenges in maintaining expected drug product quality in the global supply chain, minimising market recalls and shortages. A brief update on ICH initiative on Q12 for Lifecycle management will also be provided.

Krishnan Tirunellai

Krishnan is a pharmacist and did his Ph. D. in Biopharmaceutics from Dalhousie University, Canada. He served AstraZeneca and Patheon, in R&D and Manufacturing divisions for 6 years, and as a tenured Associate Professor, School of Pharmacy, Memorial University of Newfoundland, Canada, for 7 years. For the past 16 years Krishnan has been serving Health Canada in various capacities

including Manager of the New Drugs and Generic Quality divisions. He is presently serving the Bureau of Pharmaceutical Sciences as a Senior Scientific Advisor where he assists the Director's office in addressing various scientific issues including market recall and shortages of drug products. He has served the ICH as an expert on Q8 and Implementation Q8, 9, 10 and is presently serving the Q12 Expert Working Group.

Wednesday, June 1

GSK/CSPS Early Career Award Lecture

SPONSORED BY: GSK

Chair: Larry Lynd, University of British Columbia

Patient Engagement in Medication Adherence Research

Mary De Vera, Assistant Professor, Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver

Although disease treatment options are now better than they have ever been, it remains a challenge to ensure that patients follow and complete their treatment regimen. Medication non-adherence has been declared by the World Health Organization as an epidemic costing billions of dollars in wasted health care resources. However, research on interventions to help patients better take their medications has been inconsistent and disappointing, with the bulk of prior studies failing to explore patient perspectives around medication taking and adherence interventions.

As holder of the Professorship in Medication Adherence at UBC's Faculty of Pharmaceutical Sciences, my research focuses on quantifying the burden of non-adherence through population-based pharmacoepidemiologic studies as well as addressing the problem of non-adherence through novel approaches to adherence interventions. A particular interest is the importance of patient engagement in medication adherence research. Applying the Canadian Institute of Health Research's definition of "meaningful and active collaboration in conduct as well as knowledge translation", I will highlight novel approaches to engaging with patients in completed and current adherence research among patients with inflammatory chronic conditions.

Mary De Vera

Dr. Mary De Vera is a pharmacoepidemiologist / health services researcher and an Assistant Professor at UBC's Faculty of Pharmaceutical Sciences. She obtained an MSc and PhD from UBC's School of Population and Public Health and completed post-doctoral fellowships at University of Montreal's Faculty of Pharmaceutical Sciences and UBC's Faculty of Pharmaceutical Sciences. The theme of Dr. De Vera's research is "Medication Matters" and her goal is to improve outcomes of medication taking in different patient populations. Her current research interests are: 1) understanding medication adherence at the population level and developing and testing targeted interventions; and 2) examining the use and impacts of arthritis medications among pregnant women with arthritis. She holds career awards from The Arthritis Society and the Michael Smith Foundation for Health Research.

Wednesday, June 1

SESSION 3:

Nanomedicines Become Personal: Opportunities and Challenges

Chair: Shyh-Dar Li, UBC, and Amy Lee, Arbutus Biopharma

Image-guided Focused Ultrasound for Targeted Delivery of Drugs

Kullervo Hynynen, Sunnybrook Research Institute

[Abstract not available]

Kullervo Hynynen
Dr. Hynynen received his Ph.D. from the University of Aberdeen, United Kingdom. After completing his postdoctoral training in biomedical ultrasound also at the University of Aberdeen, he accepted a faculty position at the University of Arizona in 1984. He joined the faculty at the Harvard Medical School, and Brigham and Women's Hospital in Boston, MA 1993. There he reached the rank of full Professor, and founded and directed the Focused Ultrasound Laboratory. In 2006 he moved to University of Toronto where he led a $160 million effort to establish the Centre for Research in Image-Guided Therapeutics, a consortium between the Canadian government and Sunnybrook Hospital. He is currently the Director of Physical Sciences Platform at the Sunnybrook Research Institute and a Professor in the Department of Medical Biophysics and Cross Appointed Professor in Institute of Biomaterials & Biomedical Engineering (IBBME) at University of Toronto, Toronto, Ontario, Canada. He holds a Canada Research Chair in Imaging Systems and Image-Guided Therapy awarded by the Government of Canada and leads the Centre for Research in Image-Guided Therapeutics. Dr. Hynynen has published over 325 peer reviewed papers on basic and clinical research and has been awarded 16 patents many of which have been licensed by industry. He has been the recipient of numerous NIH and other agency grant awards, private sector research contracts; served on study sections, editorial boards, and has been extensively involved in commercializing ultrasound technology. He is a Fellow of the American Institute of Ultrasound in Medicine, the Acoustical Society of America, and was Honorary President of the 2nd International Symposium on MRI-guided Focused Ultrasound by the Focused Ultrasound Foundation. He was named the J. Eugene Robinson Awardee by the Society of Thermal Medicine, the William and Francis Fry Honorary Fellow by the International Society for Therapeutic Ultrasound and was awarded the Silver Medal by the Acoustical Society of America.

Recently awarded the IEEE Rayleigh Award (highest honor for achievement within the UFFC Society in the field of Ultrasonics).

Personalize Nanomedicines by Developing Multifunctional Nanoparticles and Identifying Therapeutic Biomarkers

Shyh-Dar Li, Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, BC.

Nanomedicine involves packaging an active drug into a nano-sized vehicle to enhance the drug delivery by improving the solubility, stability and targeting of the drug. Personalized medicine focuses on precise therapeutics for individual patients, thereby improving the efficacy and reducing the side effects. Incorporating personalized approaches into nanomedicine is one of the recent research focuses in this field. I will report the recent progress in my lab developing personalized nanomedicines via the strategies of non-invasive imaging and biomarker identification.

Shyh-Dar Li
Dr. Li is an Associate Professor at UBC Faculty of Pharmaceutical Sciences. His research focuses on developing innovative drug delivery systems to enhance cancer chemotherapy. Dr. Li's research program has been supported by CIHR. He has receive several research awards, including CSPS Early Career Award, CIHR New Investigator Award, AFPC New Investigator Award, and AAPS New Investigator Award. (shyh-dar.li@ubc.ca)

Porphysome Nanotechnology: Discovery and Road to Clinical Translation

Gang Zheng, Princess Margaret Cancer Centre and University of Toronto, Toronto, ON

Porphysomes, self-assembled from porphyrin-lipid building blocks, are unique nanoparticles with intrinsic multimodal photonic properties. The high-density packing of porphyrin bilayers enables these nanoparticles to absorb and convert light energy to heat with extremely high efficiency, making them ideal candidates for photothermal therapy and photoacoustic imaging. Upon nanostructure disruption, fluorescence and photoreactivity of free porphyrins are restored to enable low background fluorescence imaging and activatable photodynamic therapy. Here, our recent porphysome translational efforts are summarized. We have validated porphysome's multimodal theranostic utilities in different cancer types (prostate, ovarian, head & neck cancer, pancreatic and brain cancer), different tumor models (subcutaneous, orthotopic, chemically-induced and primary) as well as different animal species (mice, hamsters and rabbits). It was founded that the preferential uptake of porphysome in tumors versus adjacent normal tissues is well preserved across different tumor models. In addition, compared with any other photonic nanomaterials, porphysomes have considerably lower translational hurdles owing to their a) simple two-step synthesis, b) robust scale up following proven liposome technology, c) extremely low systemic toxicity, and d) proven biodegradable in vivo. Further, porphysome can directly chelate radioisotope copper-64 to enable quantitative and noninvasive tracking of their in vivo fate via PET imaging. Together, the simple yet intrinsic multimodal nature of porphysomes not only confers high potential for clinical translation but also represents a novel principle for designing multifunctional nanoparticles.

Gang Zheng

Dr. Zheng is a Professor of Medical Biophysics, Biomedical Engineering and Pharmaceutical Sciences at the University of Toronto, a Senior Scientist, the Joey and Toby Tanenbaum/Brazilian Ball Chair in Prostate Cancer Research at the Princess Margaret Cancer Center. He received his PhD in 1999 from SUNY Buffalo in Medicinal Chemistry. Following two year postdoctoral training in photodynamic therapy at the Roswell Park Cancer Institute, he joined the University of Pennsylvania in 2001 as an Assistant Professor of Radiology. Since moving to Canada in 2006, his research has been focused on developing clinically translatable technology platform to combat cancer. Dr. Zheng's most significant contributions are his pioneering work on activatable photosensitizers for photodynamic therapy and his discovery of porphysome nanotechnology that opens new frontiers in cancer imaging and therapy. The latter was also named one of the "top 10 cancer breakthroughs of 2011" by the Canadian Cancer Society. During the last 5 years, Dr. Zheng published 81 peer-reviewed papers, gave 79 invited lectures and had 4 issued US patents. Dr. Zheng is an Associate Editor for the Bioconjugate Chemistry since 2014 and was recently elected to the College of Fellows of the American Institute for Medical and Biological Engineering (AMIBE).

TKM-Ebola and TKM-Ebola-Guinea: Rapid Re-development of a Nucleic Acid Therapeutic in Response to the West Africa Outbreak

Amy Lee, Arbutus Biopharma Corporation, Burnaby, BC, Canada

TKM-Ebola was developed as a RNA interference (RNAi) post-exposure therapeutic for Ebola Hemorrhagic Fever Virus (HFV) infections based on a proprietary lipid nanoparticle (LNP) nucleic acid delivery platform. LNP are readily adapted for the delivery of any nucleic acid molecule and have been shown to be effective for a number of therapeutic applications: to date, nine LNP-based products have entered clinical trials. Ebola virus (EBOV) is responsible for periodic episodes of haemorrhagic fever in Central Africa that produce severe disease and up to 90% mortality in humans, and has been identified as a weaponizable biological threat.

Developed in conjunction with the US Department of Defense, TKM-Ebola utilizes LNP-encapsulated siRNA targeting mRNA transcripts coding for essential viral components EBOV RNA polymerase L protein and viral protein VP35. TKM-Ebola has undergone testing in a Phase 1 clinical trial, and was also used to treat Ebola-infected subjects under the FDA compassionate use program in the United States.

The original TKM-Ebola product targets EBOV variants from Central Africa, but it soon became clear that the recent West African outbreak differed

not only in geography but also in the genetic identity of the viral isolate involved. With viral genomic information becoming available in April 2014 in the form of viral sequence from just 3 patients (bolstered by additional sequence data releases in the months to follow), we took advantage of the rapid response nature of the LNP platform technology to develop a modified TKM-Ebola product to specifically address the West Africa outbreak. This involved adjustment of 3 nucleotide positions across the two siRNA components comprising the active drug moiety and laboratory verification of pharmacology activity. The streamlined manufacturing process for LNP subsequently enabled expeditious manufacture of clinical-grade material. The West African product, TKM-Ebola-Guinea, has subsequently demonstrated 100% survival in rhesus macaques and was selected for a controlled clinical trial in West Africa in collaboration with the World Health Organization (WHO), International Severe Acute Respiratory and Emerging Infecting Consortium (ISARIC), and the Wellcome Trust.

In this presentation, we discuss how TKM-Ebola and TKM-Ebola-Guinea illustrate the ability of the siRNA-LNP drug technology platform to be quickly and effectively directed to respond to changes in a drug target, whether that be variation in the target over time or differences between patient populations.

Amy Lee

Amy Lee is a Senior Research Director at Arbutus Biopharma (previously Tekmira Pharmaceuticals, Protiva Biotherapeutics) located near Vancouver, Canada. She has been involved in lipid nanoparticle (LNP)-enabled nucleic acid drug discovery and preclinical development for over 15 years across a diverse range of therapeutic areas, including dyslipidemia, oncology, alcohol dependence, and filovirus (Ebola, Marburg) infection. Career highlights have included the 2009 first-in-human clinical trial for the lipid nanoparticle technology platform, wherein the particles were designed to deliver apolipoprotein B-targeting short interfering RNA (siRNA) to the liver for the treatment of hypercholesterolemia, as well as participation in efforts to medically respond to the 2014 Ebola outbreak in West Africa. Currently she oversees a team of scientists focusing on animal pharmacology modeling and nucleic acid drug discovery for Arbutus Biopharma's portfolio of RNA interference and small molecule drug candidates for the treatment of chronic Hepatitis B infection, which affects 400 million people worldwide. Amy is an alumna of the University of British Columbia's Department of Microbiology & Immunology.

Selected Abstract for Oral Presentation

Polymer-Lipid Based Nanomedicine of Synergistic Drug Combination for Improving Chemotherapy of Multidrug Resistant Breast Cancer (Abstract # 85)

Rui Xue Zhang, University of Toronto

Wednesday, June 1

SESSION 4:

Broaching the Fourth Hurdle: Getting Drugs on the Formulary

Chair: Larry Lynd, UBC

Orphan Drugs - Catastrophic Drug Coverage

Fred Horne, MBA, Adjunct Professor, School of Public Health, University of Alberta; Alberta Minister of Health, 2011-2014

Ensuring equitable and affordable access to orphan drugs is a continuing challenge for federal and provincial drug plans. While often discussed as a peripheral "cost driver" in the overall context of health care systems, rare diseases affect over 3 million Canadians. Viewed from this perspective, lack of an appropriate framework to support the development, evaluation, and reimbursement of these drugs is arguably a significant public health issue that presents catastrophic implications for patients and families, and sub-optimal outcomes for health systems.

As a former Minister of Health, Fred Horne will discuss these and related issues from a public policy and payer perspective. Drawing from the Alberta experience, Canada's Rare Disease Strategy, and observations about intergovernmental discussions and initiatives focused on reducing drug costs, he will make the case that a strategic pan-Canadian approach is required, and the time is now.

Fred Horne

Fred Horne is a health policy consultant and served as Alberta's Minister of Health from 2011-2014. A frequent speaker and panelist on health system issues in Canada, he is Principal of Horne and Associates, Public Policy Consultants, and Adjunct Professor at the School of Public Health, University of Alberta.

Fred began his career in health policy over thirty years ago and has extensive experience in policy development and coordination, health system design and transformation, and stakeholder engagement. He has worked extensively with provincial governments, and research and stakeholder organizations in Canada and abroad. Organizations with which he has been associated include the Ontario Ministry of Health (District Health Council Program), Alberta Health (Director of Sustainability), the Conference Board of Canada and Mayo Clinic, among others. His work is currently focused on pan-Canadian strategies to support strategic health technology management; improved access to and integration of palliative and end-of-life care services; and pharmaceutical policy and procurement.

As Minister of Health, he was responsible for the province's $18 billion health budget, the Ministry of Health and Alberta Health Services, the province's health delivery organization and the fifth largest employer in Canada.

Fred holds an MBA from Royal Roads University and the Certificate in Dispute Resolution from York University. He currently serves on the boards of the Canadian Physiotherapy Association and the Canadian Frailty Network, among others.

Developing Specialty Drugs for a Conditional Reimbursement Environment: Is Quicker Necessarily Better?

Christopher McCabe, PhD, Department of Emergency Medicine, Faculty of Medicine and Dentistry, University of Alberta

The translational process for specialty drugs may appear to be in a constant state of change. Whilst regulatory authorities such as the FDA, EMEA and Health Canada are lowering the evidentiary hurdles through conditional licensing arrangements, health care payers are raising new hurdles, requiring different types of evidence and developing new pathways to patient access and reimbursement. Against this background, the science is moving toward increasingly targeted therapeutics and hence a larger proportion of all drugs falling into the 'Specialty Drug' category and with correspondingly challenging prices. From a distance it can seem that

the regulators and reimbursement authorities are pulling in different directions.

In this talk I will discuss the rationale behind health care payers implementing conditional reimbursement strategies and argue that, as custodians of limited population health care resources it would be both unethical and irresponsible to do otherwise. I will argue that these schemes are the mechanism by which the payers can signal the value of high quality evidence to developers, and hence prevent patients from bearing an excess proportion of the risk that is inherent in pharmaceutical research and development.

I then will describe a framework for developers to think about the trade-offs between early regulatory approval and be subject to conditional reimbursement schemes. I will describe how conditional reimbursement responses to immature evidence may actually reduce the total market value for a new technology and thus highlight the need for developers to prospectively evaluate the impact on revenues of alternative evidence development strategies.

[Bio not available]

Perspectives from a Public Drug Plan on the Challenges and Opportunities with Expensive Drugs for Rare Diseases (EDRD)

Eric Lun, PharmD, ACPR, BSc. Pharm, B.Sc., Executive Director, Drug Intelligence and Optimization, Medical Beneficiary & Pharmaceutical Services Division, BC Ministry of Health

Drug plans, both public and private, face several complex challenges with expensive drugs for rare diseases. As a decision maker, he will review the drug review process and what considerations are included in making drug listing decisions. He will also review the ongoing overall challenges with overall drug plan management and the specific challenges and opportunities with EDRDS, including the often limited clinical evidence and the often extremely high costs set by the pharmaceutical companies for these products. The opportunities to address the challenges with EDRDs will not be easily resolved and will require a broad effort by all involved stakeholders.

Eric Lun

In his current role within Medical Beneficiary and Pharmaceutical Services Division (MBPSD), Eric leads the Drug Intelligence and Optimization branch.

The branch is responsible for determining which drugs are included in the BC PharmaCare formulary through the national Common Drug Review (CDR-CADTH) process, the pan-Canadian Pharmaceutical Alliance (pCPA) negotiation process, and the provincial Drug Benefit Council (DBC) review process. The branch also is responsible for adjudicating drug funding requests through Special Authority, supporting the optimal and appropriate use of drugs in BC (e.g. supporting prescribing guidelines and academic detailing), and leading other specialty programs and initiatives.

Prior to joining MBPSD in 2007, Eric worked with the Vancouver Coastal Health Authority as Regional Coordinator, Medication Use Management. Eric has also worked as a financial research analyst for the biotech and healthcare sector (TD Securities), as a clinical pharmacist (Vancouver General Hospital), a Drug Use Evaluation pharmacist (University of Alberta Hospital), and a pharmacy lecturer (University of Technology, Jamaica).

The Complexity in Making Reimbursement Decisions around Expensive Drugs for Rare Diseases

Doug Coyle, Professor, Department of Epidemiology and Community Medicine at the University of Ottawa

In making funding decision relating to expensive drugs for rare diseases, both ethical and economics concerns have been raised. In this talk, these issues will be discussed with reference to recently available products; eculizumab for the treatment of paroxysmal nocturnal hemoglobinuria (PNH) and ivacaftor for the treatment of cystic fibrosis in people with certain mutations. The presentation will highlight the potential patient benefit associated with such treatments and the associated opportunity costs. The presentation will discuss issues relating to identifiability, rule of rescue, innovation, equity and ethics with respect to funding decisions and thus highlight the underlying complexity facing decision makers.

Doug Coyle

Doug Coyle is a health economist and Professor in the Department of Epidemiology and Community Medicine at the University of Ottawa and at the Health Economics Research Group at Brunel University where he obtained his PhD. Particular research interests include the handling of uncertainty and variability in economic evaluation and the application to treatments for rare diseases. Doug is a current member of the Ontario Ministry of Health and Long Term Care's Committee to Evaluate Drugs and Drugs for Rare Diseases Working Group.

Selected Abstract for Oral Presentation

Preferences for Donating Money to Support Drug Development Research Projects in a Sample of Canadian and U.S. Adults

Nick Dragojlovic, University of British Columbia

Thursday, June 2

Breakfast Session: Medical Marijuana

Chair: Frank Abbottd, UBC

Chemical and Genomic Analysis of Cannabis

Jonathan Page, PhD, Anandia Labs Inc., Vancouver, and Botany Department, University of British Columbia, Vancouver BC, Canada

Cannabis sativa L. (marijuana, hemp; Cannabaceae) is an ancient crop plant that produces nutritious seeds, high-quality fibre and bioactive cannabinoids, *e.g.* Delta-9-tetrahydrocannabinol (THC). We are using a combination of genomics and biochemistry to elucidate the cannabinoid metabolic pathway and to better understand the genetic organization of the genus *Cannabis*. A major experimental approach has been the use of EST and transcriptome data derived from glandular trichomes, the specialized epidermal structures that synthesize cannabinoids. We have successfully applied trichome-focused analysis to identify three enzymes of the cannabinoid pathway: hexanoyl-CoA synthetase, olivetolic acid cyclase and an aromatic prenyltransferase. A draft assembly of the ~820 Mbp genome from the marijuana strain Purple Kush, has opened up new avenues for gene discovery as shown by the identification of a novel cannabinoid synthase enzyme, cannabichromenic acid synthase. We have recently used genotyping-by-sequencing (GBS) to analyze the genetic variation in 43 hemp and 81 marijuana accessions. GBS shows that hemp and marijuana are genetically distinct, and provides insight into the differentiation of marijuana into “Indica” and “Sativa” groups. As cannabis emerges from the shadow of prohibition, genomics promises both to clarify its evolutionary history and to accelerate the development of this valuable, multi-use crop.

Jonathan Page
Jonathan has spent his career deciphering the genetic and biochemical secrets of medicinal plants, including the production of THC and other cannabinoids in cannabis. He received his PhD from the University of British Columbia (1998), undertook postdoctoral training in Germany (1998-2003) and directed a lab at the National Research Council’s Plant Biotechnology Institute (2003-2013). Dr. Page co-led the Canadian team that reported the first sequence of the cannabis genome and his work has helped elucidate the biochemical pathway leading to the major cannabinoids. He recently founded a biotechnology company, Anandia Labs, to develop new cannabis-based medicines using genomics and plant breeding. He is also an Adjunct Professor in the Botany Department at the University of British Columbia.

Medical Cannabis and Cannabinoids

Caroline MacCallum, Internal Medicine, UBC Hospital, and Bone Marrow Transplant Ward, VGH

We will start by reviewing the endocannabinoid system, cannabinoids compounds, and their evidence, then shift clinically to focus on cannabinoid uses, contraindications, routes and dosing, interactions, and side effects. We will discuss the pharmacists' role in helping their patients navigate this process.

Dr. Caroline MacCallum
Dr. MacCallum graduated from the University of British Columbia Internal Medicine Residency Program in 2013. She completed her Undergraduate Medical training in 2009 and her Bachelors of Science in Pharmacy in 2005 at Memorial University of Newfoundland, where she was born and raised. Upon graduation, she practiced Pain & Addiction Medicine at Vancouver General Hospital Complex Pain & Addiction Services, CHANGEpain Clinic, and at Heartwood Addiction Program at BC Women’s Hospital. Currently she provides inpatient care on the Internal Medicine Ward at UBC Hospital and Bone Marrow Transplant Ward at VGH; and outpatient care at BC Women’s Complex Chronic Disease Program

She is also the medical director at Greenleaf Medical Clinic; a cannabis clinic in Abbotsford, which authorizes legal Health Canada-approved medical cannabis. Her cannabis research focus is in the multimodal effects of cannabis on symptoms clusters; reducing polypharmacy, opioids and adverse drug effects; and topical application of cannabis.

In her private practice she offers group medical visits in conjunction with allied health care professionals to provide patients with additional tools to manage their complex pain. Groups include pain neurosciences with focus on pacing, CBT, and mindfulness; therapeutic movement group; sleep and nutrition groups as well as medicinal cannabis groups.

Dr. MacCallum is also passionate about student mentorship. She is the co-sponsor for the UBC Medical School Global Health Initiative on the Spiti India Project.

Thursday, June 2

Plenary Lecture 4

Chair: Corey Nislow, UBC

Genomics in Canada: From Knowledge Generation to Patient Outcomes

Ivana Cecic, Health Sector Manager, Genome British Columbia

With an ageing population and health care cost increasingly rising, the human health sector is facing many important challenges around the world. There is a pressing need to increase innovation that could lead to new and more efficacious medications in order to address key global health issues such as cancer and infectious diseases. Moreover, we have a system that is mainly focusing on diagnosis and treatment of diseases instead of focusing on prevention and health.

Thanks to the great technological advances that have taken place after the sequence of the first human genome in 2001, genomic (and all the "omic" technologies in general) tools are now offering concrete solutions to help improve the diagnosis and treatment of disease and also to promote a better understanding of disease that could help focus more on disease prevention instead of late treatment of complex and rare diseases.

After more than 10 years of investment in the field of genomics, Genome BC and the Canadian Genomic Enterprise are now moving from projects that generated knowledge about our genome and our genes, into projects that are focusing on implementing innovative genomic technologies into the healthcare system. Canada, and BC in particular, are starting to see now concrete projects where genomics is being implemented and integrated into the health care system, leading to concrete socioeconomic impact and a more efficient health care system. A series of concrete examples of the use and impact of genomics on key areas such as cancer, infectious diseases, pharmacogenomics and rare disease will be discussed in order to illustrate how the genomic revolution is changing the health care system in Canada and around the world.

Ivana Cecic

[Bio not available]

Thursday, June 2

SESSION 5:

Pharmacogenomics in the Clinic and Community

SPONSORED BY: GENOME BC

Chair: Corey Nislow, UBC

Harnessing the Power of Synthetic Lethality: Identifying and Targeting Dependencies in Cancer

Lisa Belmont, Genentech, Inc., South San Francisco, CA

In the last decade we have begun to appreciate the power and the challenges of personalized cancer medicine. The successes have predominantly focused on inhibiting pathways that are activated by mutation or amplification. However, a major challenge of developing targeted cancer therapies lies in the observation that a large percentage of oncogenic drivers are due to mutations that result in loss of function (LOF). Strategies for targeting these cancers are less direct and rely upon the identification of cancer specific vulnerabilities that arise from LOF. Our research is focused on strategies to target cancers with defects in the SWI/SNF (BAF) complex, a chromatin-remodeling complex that repositions nucleosomes. The composition of SWI/SNF complexes varies by cell type, but all complexes contain one of two mutually exclusive ATP dependent helicases, SMARCA4 (BRG1) or SMARCA2 (BRM) that disrupt nucleosome/DNA contacts to allow repositioning. Large-scale cancer sequencing efforts have revealed that 20% of all cancers harbor a mutation in at least one subunit of the SWI/SNF complex, including 10% of non-small cell lung cancers with mutations in BRG1. Loss of BRG1 renders the cancer cells dependent upon BRM for survival, making it an appealing drug target for BRG1 mutant cancers. However, there are challenges to making a selective small molecule inhibitor of BRM. As such, we are evaluating multiple approaches to targeting BRG1 cancer. The approaches include novel strategies for inhibiting BRM and running CRISPR/Cas9 dropout screens to identify additional targets in BRG1 mutant cancer.

Lisa Belmont

Dr. Belmont received her PhD from UCSF, where she determined that increased microtubule catastrophe rate is the major mechanism governing changes microtubule dynamics during mitosis. She went on to identify a novel protein that increases microtubule catastrophe rate. She then moved to UC Berkeley where she demonstrated that actin filament destabilization is due to an opening of the nucleotide-binding cleft upon phosphate release after ATP hydrolysis. Upon completion of post-doctoral research, she joined a newly formed biotechnology company and genetically engineered strains of *Kluveromyces* for direct conversion of cellulose to fuel grade ethanol. After that she returned to her roots in the cell biology and spent five years at Cytokinetics Inc. working on target validation and lead optimization for chemical inhibitors of mitotic kinesins as experimental cancer therapeutics. In 2006, Dr. Belmont moved to Genentech, where she has led biology teams to support small molecule inhibitor projects related to the cell cycle (mitotic kinases), apoptosis (Bcl-2 family antagonists), tumor metabolism (NAMPT), and epigenetic regulators. Much of the work in these groups focused on the identification of predictive biomarkers for experimental therapeutics as part of a personalized medicine initiative. The Bcl-2 antagonist, venetoclax, was recently approved for use in Chronic Lymphocytic Leukemia (CLL) patients with 17p deletion, a common deletion that removes the tumor suppressor, p53. Her lab is currently working on identification of synthetic lethal interactions in cancer to identify vulnerabilities created by loss of tumor suppressors that can be targeted with small molecule inhibitors.

Implementation of Pharmacogenomics for the Prevention of Severe Adverse Drug Reactions in Pediatric Oncology

Colin Ross, Assistant Professor of Pharmacogenomics, Faculty of Pharmaceutical Sciences, University of British Columbia; Scientist, Child and Family Research Institute (CFRI), BC Children's Hospital, Vancouver.

Adverse drug reactions (ADRs) account for an alarming 7% of all hospital admissions and are ranked as a leading cause of death in the USA. The Canadian Pharmacogenomics Network for Drug Safety (CPNDS) was established to identify, report, and solve drug safety concerns in pediatrics. Pediatric oncology is especially constrained by the problem of severe ADRs.

As an example, anthracyclines are a class of highly effective chemotherapeutic widely used to treat childhood and adult cancers. The use of anthracyclines, however, is limited by the development of serious cardiotoxicity in some patients. Candidate gene studies have suggested a pharmacogenomic component to this severe adverse drug reaction. We recently conducted a genome-wide pharmacogenomic study of anthracycline-induced cardiotoxicity and performed exploratory mechanistic studies of an emergent prioritized gene, *RARG*. Our studies indicate that RARG plays an important role in the development of anthracycline-induced cardiotoxicity.

In a multidisciplinary collaboration (e.g., clinical pharmacology, pediatric oncology, cardiology, pharmacogenetics) we have implemented a clinical research program to explore the use of pharmacogenomics as a tool for ADR mitigation in pediatric oncology in BC.

Colin Ross

Colin Ross, BSc.h (UBC), MSc (Newcastle, UK), PhD (McMaster University), is an Assistant Professor of Pharmacogenomics, Faculty of Pharmaceutical Sciences, University of British Columbia, and Scientist, Child and Family Research Institute (CFRI) at the BC Children's Hospital in Vancouver.

I grew up in the Penticton, B.C, and I am married with two boys (aged 11 and 13). My research seeks to integrate genetics with novel strategies to improve the safety and effectiveness of medications. For example, I developed a novel gene-delivery treatment for LPL Deficiency, a genetic disorder of lipid metabolism, which recently became one of the first gene-based therapies to receive regulatory approval. My research is now largely focused on the identification/ implementation of genetic factors of drug response to better guide safer and more effective individualized patient treatments. The debilitating and sometimes lethal consequences of severe adverse drug reactions are a striking problem in modern medicine. The consequences for patients who experience severe ADRs can be catastrophic. I helped establish the 'Canadian Pharmacogenomics Network for Drug Safety' (CPNDS), a network of clinicians and researchers in hospitals across Canada to identify patients that have suffered severe ADRs with the goal of developing and implementing genotype-based predictive pharmacogenomic tests to help optimize individual drug treatment.

UBC - GenomeBC - BCPhA Project

Corey Nislow, Associate Professor, Faculty of Pharmaceutical Sciences, Director of the UBC Sequencing Centre, and Tier 1 Canada Research Chair, UBC

In the year 2000 the human genome project announced the completion of the first draft human DNA sequence, a 15 year project which cost $3 billion and enormous research investment. This accomplishment, while extraordinary, failed to deliver on many of the project's promises. In retrospect the reasons are obvious. The 3 billion letters of the human genome are in fact 99.5% identical between any two individuals- it is this small fraction, approximately 3 million so-called DNA variants that distinguish individuals and determine i) our susceptibility to disease ii) our unique physiology and cognitive capacities and iii) our response to hundreds of medication. Because the best way to define cause and effect requires very high confidence correlations, in order to infer the effect of any single genetic variant on drug response, large numbers of sequenced human genomes are required. In the past three years the sequencing landscape has been transformed, and thousands of genomes from diverse populations have been collected and carefully annotated by our group and others. To use this information in practice, one needs a means to collect individual biological samples (such as saliva), deliver them to a clinically certified sequencing laboratory and return that information

(and ONLY that information) encoded within an individual's DNA sequence to tailor their medication and dose. Over the course of an 18 month Community Pharmacogenomics project we demonstrated that the logistics and infrastructure to deliver genomic information from patient to pharmacist and back again is safe, reproducible and scalable. This project represents a unique blending of clinical research with pharmacy providers and patient engagement to realize the patient benefits of using cutting-edge Pharmacogenomics research to help patients.

Corey Nislow

Corey Nislow completed his doctor of philosophy in University of Colorado. He was an American Cancer Society fellow, group leader in three biotechnology companies and senior genome scientist at Stanford University. Before joining UBC, Dr. Nislow was associate professor at the University of Toronto. In the UBC Faculty of Pharmacy he is an Associate Professor, Director of the UBC Sequencing Centre and a Tier 1 Canada Research Chair. His work on drug-gene and drug-environment interactions is broad in scope, ranging from yeast to human and, as part of an ongoing collaboration with NASA and Duke University, he has flown experiments on 4 missions to the International Space Station. Nislow is Principal Investigator for the 'Genomics for Precision Drug Therapy in Community Pharmacy' project, which demonstrated that pharmacists are well positioned to convey pharmacogenomics information to their patients and their healthcare team. He has 150 peer-reviewed publications and 6 issued patents.

Thursday, June 2

SESSION 6:

Responsive Drug Delivery Systems

Co-Chairs: Todd Hoare, McMaster University and Marc Gauthier, INRS

Selected Abstract for Oral Presentation

Complete Regression of Xenograft Tumors upon Targeted Delivery of Paclitaxel via Π-Π Stacking Stabilized Polymeric Micelles (Abstract #30)

Roy van der Meel, Utrecht University / UBC

Smart Automated Release, Because Drugs Don't Work in Patients who Don't Take Them

Adah Almutairi, University of California, San Diego

[Abstract & Bio not available]

Poly(2-oxazoline) Biomaterials

Richard Hoogenboom, Supramolecular Chemistry Group, Department of Organic and Macromolecular Chemistry, Ghent University, Krijgslaan, Ghent, Belgium. Richard.hoogenboom@ugent.be

The living cationic ring-opening polymerization of 2-oxazolines has been studied in great detail since its discovery in 1966. The versatility of this polymerization method allows copolymerization of a variety of 2-oxazoline monomers to give a range of tunable polymer properties that enable, for example, hydrophilic, hydrophobic, fluorophilic, as well as hard and soft materials. However, this class of polymers was almost forgotten in the 1980s and 1990s because of the long reaction times and limited application possibilities. In the new millennium, a revival of poly(2-oxazoline)s has arisen because of their potential use as biomaterials and thermoresponsive materials, as well as the easy access to defined amphiphilic structures for (hierarchical) self-assembly. Recent developments from our research that illustrate the potential of poly(2-oxazoline)s will be discussed in this lecture, including the preparation of defined high-molar mass polymers for use in preparation of solid dispersion as well as functional poly(2-oxazoline)s as biomaterials.

Richard Hoogenboom
Richard Hoogenboom was born in 1978 in Rotterdam (the Netherlands) and studied chemical engineering at the Eindhoven University of Technology (the Netherlands). In 2005, he obtained his Ph.D. under the supervision of Ulrich S. Schubert and continued working as a project leader for the Dutch Polymer Institute. After postdoctoral training at the RWTH Aachen with Prof. Martin Moeller and at the Radboud University Nijmegen with Prof. Roeland Nolte, he was appointed as associate professor at Ghent University in 2010 and in October 2014 he was promoted to full professor. His research interests include stimuli-responsive polymers, supramolecular polymers, and poly(2-oxazoline)s. He has published more than 260 refereed scientific articles and is associate editor for European Polymer Journal and Australian Journal of Chemistry.

"Bio-hybrid" Therapeutics

Mi Liu[1], Gregor Fuhrmann[1], Pål Johansen[2], Jean-Christophe Leroux[1], Marc A. Gauthier[3].
[1]Department of Chemistry Applied Biosciences, ETH Zurich; [2]Department of Dermatology, University Hospital Zurich, Zurich, Switzerland; [3]EMT Research Center, Institut National de la Recherche Scientifique, Varennes, QC, Canada

In comparison to neutral linear polymers, functional and architecturally complex (i.e., nonlinear) polymers offer distinct opportunities for enhancing the properties and performance of therapeutic proteins. However, understanding how to harness these parameters is challenging, and studies that capitalize on them in vivo are scarce. This presentation will cover this important topic with emphasis on two types of therapeutic proteins: ones

for which long circulation in the bloodstream is desired, and ones for which retention and/or stabilization in the gastrointestinal tract is desired.
We will first present how the modification of an enzyme with a polymer of appropriate architecture can impart exceptionally low immunogenicity (e.g., generation/recognition of antibodies in vivo), with a commensurably low loss of therapeutic activity.[1,2] Secondly, we will also discuss how the modification of an enzyme with a polymer bearing appropriate functional groups can promote its stability (and thus therapeutic activity) at different locations in the gastrointestinal tract. Furthermore, functional polymers that interact with mucin will be shown to promote retention in the upper part of the gastrointestinal tract, and thus enhance the therapeutic activity of enzymes at this location.[3] Overall, the importance of the findings will be framed with context to selected relevant diseases that stand to benefit most from the presented concepts.

[1] Liu, Tirino, Radivojevic, Phillips, Gibson, Leroux, Gauthier. Advanced Functional Materials. 2013, 23, 2007
[2] Liu, Johansen, Zabel, Leroux, Gauthier. Nature Communications, 2014, 5, 5526.
[3] Fuhrmann, Grotzky, Lukić, Matoori, Yu, Luciani, Walde, Schlüter, Gauthier, Leroux. Nature Chemistry, 2013, 5, 582

Marc A. Gauthier

Prof. Marc A. Gauthier obtained his PhD in polymer chemistry at the Université de Montréal in 2007. Following a postdoc at the Swiss Federal Institute of Technology Lausanne (EPFL), he became a Research Associate at the Swiss Federal Institute of Technology Zurich (ETHZ) in 2009. In 2013 he joined the faculty of the Institut National de la Recherche Scientifique (INRS) in Canada where his work focuses on developing new types of dynamic covalent bonds, designing therapeutic protein–polymer conjugates, establishing new technologies for drug discovery, and investigating new opportunities for physically actuating therapeutic bioconjugates
.

Thursday, June 2

CSPS Award of Leadership in Canadian Pharmaceutical Sciences Lecture

Chair: Raimar Loebenberg, University of Alberta

Pharmaceutical Research and Development, Lessons Learned

Fakhreddin Jamali, Professor, Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, AB

[No abstract]

Fakhreddin Jamali

Dr. Jamali (Doctor of Pharmacy, University of Tehran; MSc, pharmaceutics and PhD, pharmacokinetics, University of British Columbia) is a professor at the Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta. His research interests include effect of pathophysiological changes on the action and disposition of drugs, stereochemical aspects of drugs action and disposition, basic and clinical pharmacology of anti-rheumatic, analgesic and cardiovascular drugs, and toxicology of nonsteroidal anti-inflammatory drugs. He has trained 39 PhDs and published over 220 refereed articles, mainly reporting original research (H-Score, 42). For his academic achievements and research, he has been appointed as a Fellow of the Canadian CSPS, the American Association of Pharmaceutical Sciences, and the American College of Clinical Pharmacology. He has received the Killam Professorship, McKeen Cattell Memorial Award of the American College of Clinical Pharmacology, the McCalla Professorship of the University of Alberta, the McNeil Award of Association of Faculties of Pharmacy of Canada, and the CSPS Leadership Award. For his service to the public, he has been honored with the Alberta Centennial Medal and the Alberta Pharmacy Centennial Award of Distinction. Dr. Jamali has served as an expert witness as well as consultant and/or a member of the board of directors of many pharmaceutical houses. He has been a member of the Health Canada's Expert Advisory Committee on Bioavailability and Bioequivalence, and the Expert Advisory Panel on Nonsteroidal Anti-inflammatory Drugs. He is the founding president of CSPS and editor of J. Pharm. & Pharm. Sci., first open access journal in the field. He teaches pharmacokinetics and has been involved in pharmacy curriculum development.

Thursday, June 2

SESSION 7:

Drug Targeting and Targeting Drugs

SPONSORED BY: ZYMEWORKS

Chair: Robert Young, Simon Fraser University

Targeted and Stimuli-sensitive Combination siRNA/Drug Nanopreparations for Multidrug Resistant Cancer

Vladimir Torchilin, Center for Pharmaceutical Biotechnology and Nanomedicine, Northeastern University, Boston, MA, USA

Tumor therapy, especially in the case of multidrug resistant cancers, could be significantly enhanced by using siRNA down-regulating the production of proteins, which are involved in cancer cell resistance, such as Pgp or survivin. Even better response could be achieved is such siRNA could be delivered to tumors together with chemotherapeutic agent. This task is complicated by low stability of siRNA in biological surrounding. Thus, the delivery system should simultaneously protect siRNA from degradation. We have developed several types of lipid-core polymeric micelles based on PEG-phospholipid or PEI-phospholipid conjugates, which are biologically inert, demonstrate prolonged circulation in the blood and can firmly bind non-modified or reversibly-modified siRNA. Additionally, these nanopreparations can be loaded into their lipidic core with poorly water soluble chemotherapeutic agents, such as paclitaxel or camptothecin. In experiments with cancer cell monolayers, cancer cell 3D spheroids, and in animals with implanted tumors, it was shown that such co-loaded preparations can significantly down-regulate target proteins in cancer cells, enhance drug activity, and reverse multidrug resistance.

In order to specifically unload such nanopreparations inside tumors, we made them sensitive to local tumor-specific stimuli, such as lowered pH, hypoxia, or overexpressed certain enzymes, such as matrix metalloproteases. Using pH-, hypoxia-, or MMP2-sensitive bonds between different components of nanopreparations co-loaded with siRNA and drugs, we were able to make the systems specifically delivering biologically active agents in tumors, which resulted in significantly improved therapeutic response.

Vladimir Torchilin

Vladimir P. Torchilin is a University Distinguished Professor and Director, Center for Pharmaceutical Biotechnology and Nanomedicine, Northeastern University, Boston. He graduated from the Moscow University with MS in Chemistry, and obtained there his Ph.D. and D.Sc. in Polymer Chemistry and Chemistry of Physiologically Active Compounds in 1971 and 1980, respectively. In 1991, Dr. Torchilin joined MGH/Harvard Medical School as the Head of Chemistry Program, Center for Imaging and Pharmaceutical Research, and Associate Professor of Radiology. Since 1998 Dr. Torchilin is with Northeastern University. He was the Chair of the Department of Pharmaceutical Sciences in 1998-2008. His research interests include liposomes, lipid-core micelles, biomedical polymers, drug delivery and targeting, pharmaceutical nanocarriers, experimental cancer immunology. He has published more than 350 original papers (which received more than 30,000 citations), more than 150 reviews and book chapters, wrote and edited 10 books, including *Immobilized Enzymes in Medicine*, *Targeted Delivery of Imaging Agents*, *Liposomes*, *Nanoparticulates as Pharmaceutical Carriers*, *Biomedical Aspects of Drug Targeting*, and holds more than 40 patents. He is Editor-in-Chief of *Current Drug Discovery Technologies*, of *Drug Delivery*, and of *OpenNano* and on the Editorial Boards of many journals including *Journal of Controlled Release* (Review Editor), *Bioconjugate Chemistry*, *Advanced Drug Delivery Reviews*, *Molecular Pharmaceutics*. Among many awards,

Professor Torchilin was the recipient of the 1982 Lenin Prize in Science and Technology (the highest award in the former USSR). He was elected as a Member of European Academy of Sciences. He is also a Fellow of American Institute of Medical and Biological Engineering, of American Association of Pharmaceutical Scientists (AAPS), and of the Controlled Release Society (CRS), and received the 2005 Research Achievements in Pharmaceutics and Drug Delivery Award from the AAPS, 2007 Research Achievements Award from the Pharmaceutical Sciences World Congress, 2009 AAPS Journal Award, 2009 International Journal of Nanomedicine Distinguished Scientist Award, 2010 CRS Founders Award, 2012 Alec Bangham Life Achievement Award, 2013 Journal of Drug Targeting Life Achievement Award, and 2013 Blaise Pascal Medal in Biomedicine from the European Academy of Sciences. In 2005-2006 he was a President of the Controlled Release Society. In 2011, Times Higher Education ranked him number 2 among top world scientists in pharmacology for the period of 2001-2010, and his H-index according to Google Scholar is 92 with more than 43,000 citations. His research was supported by more than $20 million he received as grants from the government and industry over the last 15 years.

Advancements in Antibody Drug Conjugate Technology

Django Sussman, Ph.D., Seattle Genetics, Inc., Bothell, WA

The use of monoclonal antibodies for the delivery of anticancer drugs to tumor cells has been the subject of a great deal of investigation. The field has advanced significantly with recent approvals of antibody-drug conjugates (ADCs) for the treatment of lymphomas and breast cancer. There are several aspects in antibody-drug conjugate (ADC) design that influence activity, safety, and specificity. This talk will present recent advances in ADC development relative to the antigen target, the drug/linker combination, and the mode and multiplicity of drug/linker attachment to the antibody delivery vehicle.

Django Sussman

Dr. Sussman leads antibody engineering efforts at Seattle Genetics as Director of Protein Sciences, focusing on improving the pharmacokinetics, efficacy and tolerability of antibody drug conjugates. Prior to joining Seattle Genetics, he was an American Cancer Society postdoctoral fellow at the Fred Hutchinson Cancer Research Center where he studied the structure-function relationship in endonucleases leading to rational and computational redesigns for altered specificity. In 2000 he earned his Ph.D from the University of California – Santa Cruz in Molecular, Cellular and Developmental Biology where he solved the first crystal structure of an RNA aptamer. He obtained his BS in Molecular Biology from the University of California – San Diego in 1995.

Targeting of Solid Tumors with Bi-Specific Antibodies and Bi-Specific drug Conjugates to Induce Novel Biologies and Drug-like Properties

David Poon, PhD, Executive Director for External R&D and Alliances, Zymeworks, Vancouver, BC

A robust, developable and manufacturable bi-specific platform will be discussed as the foundation to engineer novel anti-solid tumor antibodies. Unlike combination therapies, these bi-specifics demonstrate enhanced tumor decoration, tumor diffusion and retention, internalization, and effector functions. Supported with IND-enabling *in vivo* efficacy studies, Zymeworks' lead bi-specific and bi-specific ADC programs will be presented.

David Poon

David is the Executive Director for External R&D and Alliances and has been at Zymeworks for 8 years. During this span, he held various positions including overseeing all wet-lab operations and made key contributions to the development of the Azymetric™ and AlbuCORE™ platforms. He currently oversees Zymeworks' strategic collaborations and its in- and out-licensing activities. David received his Ph.D. in Chemistry from the University of British Columbia with a focus on studying the structure-function relationship of enzymes using NMR spectroscopy.

Design, Synthesis and Evaluation of Novel Anabolic Bone Targeting Prodrugs for Treatment of Osteoporosis and Other Bone Conditions

Robert N. Young, Gang Chen and Haibo Xie
Department of Chemistry, Simon Fraser University, Burnaby, BC, Canada

Prostaglandin E2 (PGE2) is known to stimulate bone growth in vivo through agonism at the EP4 receptor. Potent and EP4-selective agonists have been described but, like PGE2 itself, suffer from systemic side effects that limit their use as stand alone drugs. We have designed and synthesized a number of bone-targeting, slow release pro-drugs wherein the EP4 agonists are conjugated with bone targeting bisphosphonates (such as alendronic acid) through enzymatically cleavable linker elements. These agents are designed to be inactive in their own rights and to bind to bone after systemic administration and then slowly release the active bone growth stimulating EP4 agonist with half times of release on the order of 4-7 days. Some of these agents also release the bone resorption inhibitor, alendronic acid through the local action of the enzymes such as cathepsin K (a protease which is released by osteoclasts .as part of the bone resorption process). Pro-drugs were synthesized in doubly radiolabeled form (with tritium on the EP4 moiety and C14 on the linker element, in order to follow and quantify the uptake, and release of the active agents. These agents have been evaluated in extensive studies in a rat model of osteoporosis and have been shown to dramatically enhance bone growth when dosed once weekly. Such agents have potential for reversing the dangerous and debilitating bone loss encountered in bone conditions such as osteoporosis that afflict millions of people around the world.

Robert Young

Robert Young earned a B.Sc. from the University of Victoria (1967) and Ph.D. from the University of British Columbia (1971). Postdoctoral studies (1971-76) at Imperial College (London), University of Adelaide (Australia) and at UBC (Vancouver). Research Associate at the Institut de Chimie des Substances Naturelles in Gif-sur-Yvette, France (1976-7) and from 1977 until 2006 worked in various capacities with Merck Frosst Canada & Co. including Vice-President and Head of the Medicinal Chemistry Department. Acting site head at the Merck Frosst Centre for Therapeutic Research (Montreal) and at MSD, Terlings Park Neurosciences Centre in the UK before taking early retirement in 2006. Dr. Young's industrial career focused on the design and synthesis of novel drugs for asthma, inflammation, osteoporosis and he is most noted for his part in the discovery of the asthma drug, Singulair™ and of the anti-inflammatory drug Arcoxia™.

Since 2007, Professor of Chemistry and Merck Frosst-B.C. Leadership Chair in Pharmaceutical Genomics, Bioinformatics and Drug Discovery in the Chemistry Department, Simon Fraser University. Current research is focused on the design and synthesis of novel pharmacological probes and proof-of-concept molecules for the discovery of new drug targets. Active research programs include, discovery of novel modulators of the androgen receptor (for treatment of prostate cancer), inhibitors is cellular "autophagy" (as anticancer therapy), molecular probes to define the mechanism of cystic fibrosis drugs and projects directed to improving bone health and treating osteoporosis. Author of more than 200 publications, review articles and patents.

Selected Honours: Order of Canada (MC), Fellow of the Royal Society of Canada, the Chemical Institute of Canada and the Canadian Society of Pharmaceutical Sciences (CSPS), Prix Galien, "Heroes of Chemistry" Award (American Chemical Society), Genome BC Leadership Award and Health Research Institute Medal of Honour. President of the CSPS (2012-2013).

Selected Abstract for Oral Presentation

A First Report of an Intravesical Therapy with Activity in a Muscle Invasive Bladder Cancer Xenograft Model (Abstract # 83)

Clement Mugabe, CDRD

Thursday, June 2

SESSION 8:

Health Sustainability Evidence

Chair: Mark Harrison, UBC

Role of Patient Reported Outcome Measures (PROMs) in the Ongoing Evaluation of Treatment and Reimbursement

Stirling Bryan, Professor, School of Population & Public Health, and Director, Centre for Clinical Epidemiology & Evaluation (C2E2), UBC

A major driver of cost growth in health care is the rapid increase in the utilization of existing technology and not simply the adoption of new technology. Health economists and their HTA colleagues have become obsessed by technology adoption questions and have largely ignored 'technology management' questions. Technology management would include the life-cycle assessment of technologies in use, to assess their real-world performance, making use of routinely collected data on patient-reported outcomes (PROMs). Such a change in focus would allow health economists and health technology assessment analysts to make a more significant contribution to system efficiency through rebalancing their efforts away from technology adoption questions towards technology management issues.

Stirling Bryan
Dr. Stirling Bryan is an economist with a career-long specialization in health care. His early career was spent in the UK, with appointments in London and Birmingham. In 2005 he was awarded a Commonwealth Fund Harkness Fellowship and spent a year at Stanford University, and then moved to Canada in 2008. He is a Professor in UBC's School of Population & Public Health, and Director of VCH's Centre for Clinical Epidemiology & Evaluation. His research seeks to inform policy and practice. For example, in the UK he had an extensive involvement with the National Institute for Health & Care Excellence (NICE), and in Canada he chairs CADTH's Health Technology Expert Review Panel, advising on coverage recommendations for devices, procedures and programs.

Patient Reported Outcome Measures (PROMs) and Patient Decision Making

Mark Harrison, Assistant Professor, Faculty of Pharmaceutical Sciences, University of British Columbia

This talk will discuss opportunities to improve decision making at the patient/physician level by providing evidence from routinely collected PROMs. There is increasing focus on unnecessary, unwanted and inappropriate treatment resulting in waster in the delivery of health care. Examples will be discussed which highlight how PROMs could contribute to a more efficient health care system by supporting patient decisions and providing feedback on the expected outcomes and variability in outcomes to inform clinical practice and decision making.

Mark Harrison
Dr. Mark Harrison is Assistant Professor at the Faculty of Pharmaceutical Sciences, University of British Columbia (UBC), where he leads the Initiative for Sustainable Health Care, and Scientist at the Centre for Health Evaluation and Outcomes Sciences (CHEOS) at St. Paul's Hospital, Vancouver. Dr. Harrison is a health economist and epidemiologist whose methodological and research interests lie in policy evaluation, patient and physician decision making and preferences for healthcare interventions, and the measurement and valuation of health. Dr. Harrison is applying advances in research, education, and practice in these areas to the economic principles of health care sustainability. He has been awarded the AFPC New Investigator Research Award for 2016.

Dr. Harrison has a long-standing interest in the study of chronic disease. He is currently involved in projects investigating perspectives of health care providers, patients and at-risk people on preventative treatments for rheumatoid arthritis, policy evaluations of pharmacist medication reviews and

accelerated integrated primary and community care programs for people with chronic diseases. His policy work uses the rich administrative data sources available in British Columbia and builds on his track record in evaluating policy interventions in the UK. Before moving to UBC, he worked at the University of Manchester (UK) on a range of projects, including evaluating the impact of a national pay for performance schemes to improve the quality of primary care for chronic diseases, the use of patient-reported outcome measures to evaluate surgical outcomes, and strategies to improve the communication of risk and uncertainty in physician-patient interactions.

Dr. Harrison has a first-class Honors degree in Business and Management Sciences (University of Bradford, 2000), and an MSc (University of Edinburgh, 2002) and PhD (University of Manchester, 2008) in Epidemiology. He began his research career with the Arthritis Research UK Epidemiology Unit in 2002, and then following the completion of his PhD, at the Manchester Centre for Health Economics, both at the University of Manchester. He also served as an adviser for the National Institute of Health Research (NIHR) Research Design Service for North West England. Dr. Harrison has a strong publication record with 42 publications, 22 as lead author.

PROMs in Action: Changing Outpatient Asthma Care by Individualised Approach to Medication Adherence

Mohsen Sadatsafavi, Academic Health Economist and Outcomes Researcher, Faulty of Medicine, UBC

Despite the availability of very effective medications, the reality of asthma care is highlighted by poor outcomes mainly due to low adherence to medications. There are many different reasons for low adherence, ranging from lack of belief in efficacy to barriers to access to side effects of treatments. It is therefore unlikely for a 'one-size-fits-all' approach to improving adherence to be effective. Individualized approaches based on each patient's needs and values need to be implemented, requiring a close connection between patient and the care provider. This presentation highlights the design of a clinical trial which is under way in British Columbia that tests the feasibility, efficacy, and effectiveness of a novel, patient-centred, pharmacist-based adherence improvement intervention and discusses the role of PROMs in this context.

Mohsen Sadatsafavi
Dr. Sadatsafavi is an academic health economist and outcomes researchers in Faulty of Medicine, University of British Columbia (UBC). He has a MD degree, a MHSc degree in epidemiology, and a PhD in outcomes research. Mohsen is the leader of the health economics platform of CRRN. The vision of his program of research is improving patient outcomes and efficiency of health care delivery in Canada through enabling evidence-informed decision making at all levels of care.

Patient Reported Outcome Measures (PROMs): Do you Measure all that I Experience?

Cheryl L. Koehn, Founder and President, Arthritis Consumer Experts

Based on a 2016 Cochrane Collaboration meta-analysis, patient reported outcome measures (PROMs) in RA studies over the past 15 years reflect the existing RA Core Set measures. Yet, a number of outcomes from other health domains of concern to patients are rarely reported, thus evidence is lacking on their effect at the individual and society levels. These include fatigue, psychological status, productivity losses, sleep disturbance, coping, among others.

This talk will focus on the challenge and opportunities of broadening the core set of RA PROMs from the patient perspective.

Cheryl Koehn
Ms. Koehn is a person living with rheumatoid arthritis. Diagnosed 27 years ago, she broke new ground by creating the first grassroots arthritis organization focusing on the basics of patient rights: education and advocacy. She founded and remains the president of Arthritis Consumer Experts and JointHealth™ family of programs, the first of their kind in Canada, and co-authored *Rheumatoid Arthritis: Plan to Win*, published by Oxford University Press in 2002. She conceived of and led development of the first robust iTunes arthritis apps. As a volunteer leader, her remarks from the floor during the *Arthritis 2000* conference have been widely recognized as the catalyst for the creation of the federal research-based Canadian Arthritis Network. Ms. Koehn has been a standard bearer and

role model for the inclusion of patients in all important discussions and decisions related to arthritis for the past 25 years and today stands as the longest serving leader in the arthritis community. Most recently, she was selected a YWCA Women of Distinction 2016 nominee in the field of Health and Wellness.

Selected Abstract for Oral Presentation

How is Uncertainty in Risks and Benefits Presented in Patient Decision Support Interventions? (Abstract # 64)

Madelaine Bell, UBC

Thursday, June 2

SESSION 9:

JOINT Session with AFPC

Chair: Simon Albon, UBC

Integrating Pharmaceutical Sciences into a Pharm D Curriculum

Scott Singleton, Associate Professor, UNC Eshelman School of Pharmacy, University of North Carolina at Chapel Hill

The UNC Eshelman School of Pharmacy is transforming its doctor of pharmacy program in response to changing societal and workforce needs as well as increasing global demand for non-cognitive, meta-cognitive and learning-related cognitive skills development in pharmacy education. The linear curriculum based on classroom lecture is relatively ineffective and long outdated in a digital world where content is readily accessible. To cultivate the necessary behaviors, skills, attitudes and habits of mind, students must learn by doing through direct patient care and service learning, leadership opportunities, and hypothesis-driven research or quality improvement-driven inquiry. Our school's new curriculum launched in August, 2015. The new 4-year PharmD program emphasizes experiential learning throughout: students spend 6 months in pharmacy practice experiences prior to the 4th year, which is fully experiential. The didactic elements of the curriculum were completely redesigned to emphasize learning outcomes that complement patient care experience through active learning and pedagogies of engagement. A third key element of the new curriculum focuses on advanced inquiry, including innovation, complex problem-solving, and scholarship. We will describe our systems approach to curriculum transformation at the school, highlight the proposed new curriculum and share early examples and lessons learned.

Scott Singleton
Scott Singleton is an associate professor and vice chair of the Division of Chemical Biology and Medicinal Chemistry in the UNC Eshelman School of Pharmacy at the University of North Carolina at Chapel Hill. He fosters a school-wide culture of educational innovation and excellence by leading the Academy for Pharmacy Teaching and Learning Excellence. He also co-leads his school's Curriculum Transformation Steering Committee that is working to transform how professional pharmacists are educated. Scott is an award-winning teacher of organic chemistry, biochemistry, and medicinal chemistry, and co-founded Synereca Pharmaceuticals. He holds a BA in chemistry and biology from Trinity University in San Antonio, Texas, and a PhD in organic chemistry from the California Institute of Technology.

Friday, June 3

Breakfast Lecture

SPONSORED BY: AGILENT

Chair: Marcus Kim, Agilent

Quantitative Mass-Spectrometry Metabolomics for Direct Biochemical Phenotyping

Adam Rosebrock, Assistant Professor, Donnelly Centre for Cellular and Biomolecular Research and Department of Molecular Genetics, University of Toronto

Comprehensive analysis of intracellular small molecules, or "metabolomics", is emerging as a powerful tool for measuring the biochemical state of cells and tissues. My group is using a combination of mass spectrometry metabolomics, genetics, and big data analytical techniques to build a quantitative understanding of the biochemical wiring of cells across diverse cellular states. In contrast to the static maps of reactions that adorn textbooks and wall-charts, metabolism is a dynamic, regulated process that changes across space and time as cells grow, divide, and face diverse environmental conditions. I will discuss how my lab is leveraging patterns of metabolic response to identify and understand regulation of pathways and how we are linking changes in biochemical phenotype back to genotype.

Direct measurement of biochemical state provides a view that is orthogonal to genomic and proteomic tools. I will describe several of the analytical and software tools my lab has developed to overcome the challenges posed by the chemical diversity of metabolism, and our methods for quantitative metabolomic analysis. I will use of these approaches across species to better understand the regulation of central metabolism in model systems ranging from microbes to mammalian tumors.

I will describe how we are using our quantitative metabolomics approach to characterize the biochemical phenotypes resulting from small molecule treatment, and our efforts to use these phenotypes to understand mechanism of action as well as generate predictive "fingerprints" of drug MoA.

Adam Rosebrock

Dr. Adam Rosebrock is an assistant professor in the Donnelly Centre for Cellular and Biomolecular Research and Department of Molecular Genetics at the University of Toronto, Canada. He has had longstanding interest in using "big data" to address fundamental biological challenges. The focus of his research is on understanding the regulation of gene expression and biochemical activities that underlie cell division, growth, and survival across diverse external states. The Rosebrock lab actively develops new experimental and analytical methods and builds genetic, hardware, and computational tools to enable high-throughput and high-content biology, with particular emphasis on quantitative flow cytometry and mass-spectrometry metabolomics.

Friday, June 3

SESSION 10:

Analytical Innovation to Support Precision Medicine and Biologicals Development

Co-Chairs: Christoph Borchers, University of Victoria, and David Kwok, BRI Bioipharmaceutical Research Inc.

Distinguishing Leucine and Isoleucine Residues in De novo sequencing of mAbs using Nano LCMS^n: A Potential to Replace Edman Degradation

Dhanashri Bagal, Eddie Kast, and Ping Cao, Discovery Attribute Sciences, Amgen Inc., South San Francisco, California 94080, United States

Monoclonal Antibodies (mAbs) are large heterogeneous molecules that not only make exceptional therapeutic candidates, but also make attractive tools for research and diagnostic applications. *De novo* sequencing of mAbs, though challenging, becomes necessary when the original cell line or the cDNA is unavailable. An important feature in sequencing of mAbs is the discrimination of isobaric residues (Xle); Leucine (Leu) and Isoleucine (Ile). An incorrect identification of Xle site especially in the complementarity determining regions (CDR) can severely affect the mAb efficacy. Even though mass spectrometry (MS) plays a crucial role in sequencing of mAbs, distinction between Ile/Leu residues still remains challenging by MS alone. Multistage fragmentation (MS^n) in the mass spectrometer can provide enough evidence for Ile/Leu discrimination. However, all methods reported thus far utilize direct infusion, demanding peptide enrichment which can be labor-intensive. Here we report an online nanoLC-MS method, utilizing bottom up mass spectrometry and multistage fragmentation, which depending on the nature of the peptide exploits either generation of a 69Da ion from Ile or formation of unique *w*-ions employing ETD-HCD to discriminate between Leu and Ile. This sensitive, rapid and reliable method can easily be incorporated in the *de novo* sequencing MS workflow for accurate determination of Xle especially for the CDR region.

Dhanashri Bagal

Dhanashri Bagal is currently a Scientist in the Discovery Attribute Sciences group at Amgen located in South San Francisco. Dhanashri received her M.S. degree in Chemistry at the University of Georgia in 2006 and joined Amgen in that same year. Currently at Amgen she focusses on protein characterization and supports proteomics research programs to understand disease pathways and to identify and validate therapeutic targets. She is also involved in native mass spectrometry efforts for the characterization of non-covalent complexes and intact protein assemblies especially membrane proteins.

ImmunoMALDI MS as a Diagnostic Tool for Primary Aldosteronism

Michael Chen MD MSc, McGill University, Department of Diagnostic Medicine, Jewish General Hospital, Montreal, Quebec

Introduction: Primary aldosteronism is by far the most common form of secondary hypertension accounting for approximately 10% of all hypertensive patients. Screening with plasma renin level is crucial, as early diagnosis is associated with cardiovascular risk reduction and better patient outcome. This study compares a novel iMALDI plasma renin activity (PRA) assay against two clinical methods using patient samples.
Methods: 140 patient samples were collected for comparison on four different instruments. PRA were determined using Diagnostics Biochem Canada (DBC) ELISA, iMALDI, and LC-MS/MS (AB Sciex). PRA determination by iMALDI was done by two different MALDI-TOF instruments.
Results: Our clinical specimens had PRA results ranging from 0.03 ng/L/s to 5.94 ng/L/s as measured by the DBC ELISA PRA assay, with 45% of patients in the low renin state.

The iMALDI PRA assay showed excellent correlation with two clinical methods. Regression analyses showed R-squared value ≥ 0.92 and ≥ 0.95, when iMALDI PRA assay was compared to the ELISA and LC-MS/MS assays, respectively. Ninety-Six samples were quantitated by iMALDI PRA assay using two MALDI-TOF instruments, yielding an R-squared value ≥0.99. DBC ELISA PRA assay also revealed excellent correlation when compared to the LC-MS/MS method, with an R-squared value ≥0.92.
Conclusion: Clinical implementation of the high-throughput iMALDI PRA assay will still require reference ranges, and cost-effectiveness studies. But through optimization of reagents, protocols, robotic systems, and software, the entire iMALDI platform for PRA determination has been automated into a robust, and user-friendly diagnostic platform applicable for use in clinical laboratories.

Michael Chen
Dr. Michael Chen is a medical biochemist in the department of diagnostic medicine at the Jewish General hospital in Montreal. He received his medical degree from McGill University in 2011, followed by postgraduate residency in Medical Biochemistry at Jewish General Hospital in Montreal. In 2015, Dr. Chen received his master degree in Experimental Medicine. His research interests are focused on clinical method validation and translational proteomics. Dr. Chen is currently a member of the Scientific Committee of Mass Spectrometry Applications for Clinical Lab.

Understanding Biotransformations of a Therapeutic mAb and the Impact on Clinical PK Assay Development

Luna Liu, Jenny Li, Mauricio Maia, Mary Mathieu, Ihsan Nijem, Rebecca Elliott, Surinder Kaur, and Keyang Xu, Genentech, Inc., South San Francisco, CA

Biotransformations are known to occur to therapeutic monoclonal antibodies (mAbs) in vivo, which may lead to changes in certain properties of the molecules. When the modification takes place in the CDR regions of the mAb, it may affect its binding to the capture or detection reagents (such as target antigens or anti-ID mAbs) used in its pharmacokinetic assay. However, such potential impact by the mAb biotransformations was largely unrealized or ignored in the conventional method development process, which relies primarily on testing the recovery of spiked reference standard. We present a case study, where a peptide-based immuno-affinity capture LC-MS/MS method using the target antigen as a capture reagent was developed to quantify a therapeutic mAb in human serum. Surprisingly, even though the same capture reagent was used, two different capture procedures, stepwise vs. semi-homogeneous, yielded significantly different results in measuring drug concentrations. This phenomenon was unexpected as it was generally believed that the step of immuno-affinity capture in LC-MS/MS served primarily for the analyte enrichment, and the degree of specificity offered by the capture reagent might not be critical. Further experiments were conducted to investigate whether biotransformations of the mAb in vivo might account for the discrepancy in the measured drug concentrations. Characterization of the mAb dosed in the cynomolgus monkeys and the patients revealed three deamidation/isomerization sites in the CDR regions of the mAb. Evidences indicated that these biotransformations contributed to the differences observed in the behavior of the mAb against the capture reagent used in the PK assays. This case study demonstrates the importance of gaining insights into the in vivo biotransformations of antibody therapeutics. Potential impact from biotransformations should be carefully assessed to ensure the development of an appropriate immuno-affinity capture LC-MS/MS clinical PK assay for accurate measurement of recombinant mAb therapeutics

Luna Liu
Luna Liu is currently a Principle Scientific Researcher in BioAnalytical Sciences (BAS) at Genentech, a member of the Roche group, in South San Francisco, California. She received her B.S. degree in Chemistry from Shanxi University, China and her M.S. degree in Analytical Chemistry from West Virginia University, Morgantown, West Virginia. Luna has over twenty years of pharmaceutical and biotechnology industry experience. Since joining Genentech in 2007, she has been focused on developing and applying mass spectrometry-based techniques to qualitatively and quantitatively study small molecule drugs, monoclonal antibodies (mAbs) and antibody-drug conjugates (ADCs) both *in vitro* and *in vivo*. She and her group have developed and utilized innovative bioanalytical approaches, e.g., affinity capture LC-

MS to gain novel insights into biotransformations and pharmacokinetics of complex biotherapeutics such as ADCs in biological fluids/tissues for nonclinical and clinical studies. Such data is proven essential for understanding the ultimate fate of biotherapeutics *in vivo* and critical for molecule selection and to support regulatory filings. Prior to joining Genentech, Luna worked as a Scientist in Drug Metabolism and Pharmacokinetics (DMPK) Department at Renovis. She also worked at biotechnology and pharmaceutical companies, including Sugen, Scios, and Oread, where she was responsible for LC-MS/MS method development and high-throughput sample analysis to support efficacy, pharmacokinetics and toxicity studies of various programs.

Multiplexed Absolute Protein Quantitation by LC/MRM-MS for Clinical Research

Christoph H. Borchers, University of Victoria - Genome BC Proteomics Centre and Dept. of Biochemistry and Microbiology, University of Victoria, BC Canada

Mass spectrometry is now poised to make major contributions to personalized method in the area of biomarker discovery and validation. Biomarker validation -- long the "bottleneck" in the biomarker pipeline -- has now become feasible because of advances made in quantitative proteomics. Large-scale quantitation projects are now possible because of the development and standardization of highly-multiplexed and accurate quantitative proteomics methods, such as multiple reaction monitoring (MRM), for the simultaneous targeting of large numbers analytes. MRM assays have now been developed for hundreds of proteins for different species in different biological specimen, e.g. blood plasma, urine, CSF, saliva, and DBS. My laboratory has developed many of these into kits for the use by non-experts in mass spectrometry. Recently, we have been working on extending the scope of these MRM-based assays to include mouse proteins, since the mouse is the most commonly used model for human diseases.

Christoph Borchers

Dr. Borchers received his B.S., M.S. and Ph.D. from the University of Konstanz, Germany. After his post-doctoral training and employment as a staff scientist at NIEHS/NIH/RTP, in North Carolina, he became the director of the UNC-Duke Proteomics Facility and held a faculty position at the UNC Medical School in Chapel Hill, NC (2001-2006). Since then, Dr. Borchers has been employed at the University of Victoria (UVic), Canada and holds the current positions of Professor in the Department of Biochemistry and Microbiology and the Don and Eleanor Rix BC Leadership Chair in Biomedical and Environmental Proteomics. He is also the Director of the UVic – Genome BC Proteomics Centre, which is a member of the Genome Canada funded Genomics Innovation Network. Dr. Borchers is also appointed as Professor at McGill University in the Department of Oncology, Montreal, QC and received there the Segal Chair in Molecular Oncology at the Jewish General Hospital of the McGill University.

His research is centered around the improvement, development and application of proteomics technologies with a major focus on techniques for quantitative targeted proteomics for clinical diagnostics. Multiplexed LC-MRM-MS approaches and the immuno-MALDI (iMALDI) technique are of particular interest. Another focus of his research is on technology development and application of the combined approach of protein chemistry and mass spectrometry for structural proteomics. Dr. Borchers has published over 200 peer-reviewed papers in scientific journals and is the founder and CSO of two companies, Creative Molecules. Inc. and MRM Proteomics Inc. He is also involved in promoting proteomic research and education through his function as HUPO International Council Member, Past Scientific Director of the BC Proteomics Network and Vice-President, External of the Canadian National Proteomics Network.

Friday, June 3

SESSION 11:

Protein and Peptide Delivery

Co-Chairs: Brian Amsden, Queen's University, and Larry Unsworth, University of Alberta

Selected Abstract for Oral Presentation

Development of a Segmented Intravaginal Ring for the Combination Delivery of Hydroxychloroquine and siRNA-encapsulated Nanoparticles as a Novel Strategy for Preventing HIV Infection (Abstract #33)

Yannick Traore, University of Manitoba

The Eyes Have It - Shifting Paradigms in the Delivery of Drugs to the Eye

Heather Sheardown, Professor, Department of Chemical Engineering, Faculty of Engineering. McMaster University, Hamilton ON Canada

Traditional methods of delivery of drugs to the eye include eyedrops and more recently injection of therapies into the vitreous cavity of the eye. While the former is well accepted, the inability to target intraocular tissues and significant losses of the active agent make this a suboptimal method. As well, eye drop therapies are limited by patient compliance. Direct injection into the back of the eye, while effective, has a high incidence of complications and is therefore only useful for treatment of certain advanced conditions. It is clear that there is a real need for better methods of drug delivery. This talk will focus on novel methods of drug delivery to the eye that overcomes some of these issues and the challenges faced by each of these methods, including some discussion of the new materials that are being used to facilitate delivery. Mucoadhesive materials have the potential to increase the residence of drugs in the precorneal tear film, thereby decreasing the need for frequent drop instillation. However, turnover of the cells of the precorneal epithelium remains a limiting factor. Contact lens based drug delivery has shown promise in the lens wearing population but may not be appropriate for patients who do not currently wear lenses. Insertable scaffold materials can be placed in the back of the eye to facilitate long term drug release. However, removal, both at the end of the useful life of the device and in the event of complications will be discussed. In situ gelling materials show significant promise for maintaining therapeutic concentrations over a long time period. Targeted systems which use light as well as other methods to facilitate release are also underdevelopment. These methods will lead to a paradigm shift in ocular drug therapy.

Heather Sheardown
Dr. Sheardown (PhD, Chemical Engineering and Biomedical Engineering, University of Toronto, BEng, Chemical Engineering, McMaster University) is a professor in the Department of Chemical Engineering at McMaster University. She joined the Faculty of Engineering at McMaster in 1998, and served as Associate Dean (Graduate Studies) from 2009-2013. She holds an adjunct appointment at the School of Optometry at the University of Waterloo.

Her research interests are focused primarily on the development of biomaterials and drug delivery systems for treating ocular disorders. Her previous studies have included work on the development of novel contact lens materials, artificial cornea and intraocular lens materials and on the development of novel methods of delivering drugs to the eye. She has published over 120 refereed articles, has been an invited speaker at many conferences, and has trained 10 PhDs. She is the Scientific Director of the 20/20 NSERC Ophthalmic Materials Strategic Network and has led a number of other initiatives related to development of new materials in the eye. She was awarded the McMaster University Innovator of the Year award and has been recognized as the Hamilton Halton Engineer of the Year. She sits on a number of grant panels for NSERC and CIHR. She has served as a consultant to or worked with a number of companies in the field of ophthalmic materials and drug delivery as well as to Health Canada. She has served as associate editor and on the editorial boards of several journals.

Hollow Metallic Microneedles for Intradermal Delivery

Boris Stoeber, Department of Mechanical Engineering and Department of Electrical and Computer Engineering, The University of British Columbia, Vancouver, Canada

Microneedles are biomedical microdevices that provide a pathway across the skin barrier to exchange fluids or compounds with the body for drug delivery or biosensing. This talk will give a brief introduction into this field. The effectiveness of microneedles for intradermal drug delivery has been demonstrated in clinical trials, and it has been shown that there are several applications that benefit from delivery into the skin compared to intramuscular delivery. In addition, it has been shown that intradermal drug delivery using hollow microneedles can be painless. Different types of microneedles have been developed for different delivery strategies. This talk highlights some of the research results on microneedles achieved at the University of British Columbia.

Boris Stoeber
Boris Stoeber received the electrical engineering Diploma from the Technische Universität Darmstadt, Darmstadt, Germany, in 1998, the general engineering Diploma from the École Centrale de Lyon, Ecully, France, in 1998, and the Ph.D. degree in mechanical engineering from the University of California, Berkeley, in 2002. From 2003 to 2005, he was a Postdoctoral Scientist in chemical engineering at the University of California, Berkeley. Since 2005, he has been with the Department of Mechanical Engineering and the Department of Electrical and Computer Engineering at the University of British Columbia, Vancouver, BC, Canada, where he is an Associate Professor. He holds the Canada Research Chair for Microfluidics and Sensing Technology, and he is an Associate Editor for the IEEE Sensors Journal. His research interests include microflow control strategies, flow physics of complex microflows, microflow imaging methods, microoptical devices, sensing technology, biomedical microdevices, and fabrication techniques for microelectromechanical structures. Technology developed through his research is being commercialized by several start-up companies in California and in British Columbia.

New Strategies for Protein Delivery from Degradable Microspheres

Brian Amsden, Professor, Department of Chemical Engineering at Queen's University

Proteins are an important drug class because of their potential to treat a wide range of conditions. Compared to small drug entities, protein therapeutics are highly specific in their action, and are expected to be less toxic than synthetically derived molecules as well as to behave more predictably *in vivo*. They thus represent a significant potential market. Because of the stability requirements of proteins and the barriers to their absorption by other conventional routes such as oral, nasal, buccal, and transdermal, the route of administration for many therapeutic proteins is currently parenteral. However, parenteral delivery may not be suitable for a number of protein drugs. Most therapeutic proteins have a short *in vivo* half-life and, upon injection, are unevenly distributed in the interstitial fluid and unable to reach the desired physiologic sites. They may also bind unselectively to cellular receptors and thus cause undesirable side effects. Furthermore, many therapeutic proteins are produced locally to act on cells in the immediate environment and are required at the local tissue site for a prolonged period of time. Thus, administration regimens typically consist of multiple injections, often at supraphysiologic concentrations, which presents potential problems with patient compliance and possible complications when administered in a non-clinical setting. A long-term continuous and localized protein drug delivery depot could therefore provide numerous and distinct advantages. In this talk I will discuss the potential of utilizing low melting point biodegradable polymers to fulfill the requirements of an effective therapeutic protein formulation for long-term delivery.

Brian Amsden
Brian Amsden obtained his PhD in Chemical Engineering in 1996, in the area of therapeutic protein delivery from hydrogels and polymer microspheres. Following his PhD, he worked for Angiotech Pharmaceuticals in Vancouver as a Research Associate, leading projects involving the formulation of paclitaxel for localized delivery. He left Angiotech to join the Faculty of Pharmacy at the University of Alberta in 1997, and is currently a Professor in the Department of Chemical Engineering at Queen's University where he has been since July 2000. His current research interests

include the development of biodegradable elastomers, hydrogels, and low viscosity hydrophobic polymers for the local delivery of small molecules, peptides and proteins, and stem cells, and as scaffolds for soft and connective tissue regeneration. He is the Director of CREATE Connect Soft Connective Tissue Regeneration Network and a principal investigator in the CREATE Biointerfaces Network. He has received the Alberta Health Foundation for Medical Research Independent Establishment Award, the Ontario Premier's Research Excellence Award, the Queen's University Chancellor's Research Award, the Ontario Centres of Excellence Award of Excellence for Research Collaboration and Commercialization, and has been named Fellow Biomaterials Scientists and Engineers.

Bioinspired and Nanotechnology-Enabled Protein/Peptide Drug Delivery for Diabetes and Diseases in the Brain

Xiao Yu (Shirley) Wu, PhD, FAAPS, Director of Advanced Pharmaceutics & Drug Delivery Laboratory, Leslie Dan Faculty of Faculty of Pharmacy, University of Toronto, Ontario

Proteins/peptide drugs have been used for treatment of various diseases, such as diabetes and cancer, and gained increasing interests as modern therapies. However, delivering biologic agents to the intended targets at effective levels on demand faces tremendous challenges. Protein/peptide drugs usually have very short life-time, are prone to denaturation and enzymatic degradation, and unable to cross the blood-brain barrier (BBB). Dr. Wu's Advanced Pharmaceutics and Drug Laboratory has developed nanotechnology-based delivery systems that mimic biological systems in the regulation of hormone release or transport of large molecules to the brain. In this presentation, Dr. Wu will use two examples of bioinspired and nanotechnology-enabled delivery systems designed in her laboratory, i.e., a glucose-responsive closed-loop insulin delivery implant and a BBB-crossing nanoparticle system, to discuss how to mitigate the problems of protein/peptide drug delivery for the treatment of diabetes and diseases in the brain.

Xiao Yu (Shirley) Wu

Dr. Xiao Yu (Shirley) Wu is a full Professor and elected Fellow of American Association of Pharmaceutical Scientists (AAPS). She was trained in polymer science and engineering and earned her PhD degree in Chemical Engineering with a thesis on polyelectrolytes and stimulus-responsive nanohydrogels. After over two-year postdoctoral research in pharmaceutics and drug delivery, she joined the Faculty of Pharmacy at the University of Toronto in 1994 as a tenure-track faculty member and promoted to Full Professor in 2006. During her 22 year academic career, Dr. Wu has directed a well-funded innovative research program and become an internationally recognized expert and leader in controlled release dosage forms and novel drug delivery systems and delivery strategies. She is also a dedicated educator who has played a leading role in teaching pharmaceutics and drug delivery in the faculty at both graduate and undergraduate levels in past two decades. She has provided excellent multidisciplinary training in pharmaceutics, drug delivery and drug development to ~140 graduate students, undergraduate research students, and postdoctoral researchers working in her laboratory. She has extensive collaborations with scientists in academia and pharmaceutical industry. Dr. Wu has published >380 journal papers, book chapters, conference proceedings and abstracts and has delivered >100 invited presentations. She is a co-inventor of 25 issued or pending patents worldwide. Her current research projects include the design and *in vitro*/*in vivo* evaluation of blood-brain barrier-penetrating nanoparticles for therapy and imaging of brain cancer and CNS diseases, synergistic drug combination nanomedicine for treatment of multidrug resistant and metastatic breast cancer, hybrid bioreactive nanoparticles for remodeling tumor microenvironment and improving tumor therapy, intelligent polymer and nanotechnology-enabled closed-loop insulin delivery implant, and computer-aided design of controlled release drug delivery systems.

Poster Session 1

CSPS and CC-CRS Posters

AFPC Posters

Wednesday, June 1

Poster Session 1

Wednesday, June 1

Biomedical Sciences

1. Can HIF-1α Silencing Overcome Hypoxia Induced Conversion of Triple Negative Breast Cancer to More Tumorigenic and Drug Resistant Phenotype?

Hoda Soleymani Abyaneh, Nidhi Gupta, Raymond Lai, Afsaneh Lavasanifar.
Faculty of Pharmacy and Pharmaceutical Sciences, Faculty of Medicine and Dentistry, University of Alberta, Edmonton, Canada

Purpose: The long-term objective of this study is to assess the role of hypoxia inducible factor alpha 1 (HIF-1α) as a therapeutic target in triple negative breast cancer. For this purpose, we have first investigated the effect of hypoxia on the conversion of MDA-MB-231 cells to more tumorigenic and resistant phenotype. The effect of HIF-1α knockdown by small interfering RNA (siRNA) on this phenomenon was then investigated.
Methods: Parental MDA-MB-231 and its two subsets sorted based on responsiveness to a Sox2 regulatory region (SRR2) reporter were used. The cell subset responsive to SRR2 reporter (RR cells) is found to be significantly more tumorigenic than the reporter unresponsive (RU) cells. Lipofectamine complexed HIF-1α siRNA was incubated with cells and the expression of HIF-1α and its downstream proteins under hypoxia were analyzed by immunoblotting. Conversion of RU to RR cells under hypoxia was investigated by measuring the level of GFP expression using Flow Cytometric analysis and luciferase assay. Lastly, the effect of HIF-1α knockdown on the conversion of RU to RR cells under hypoxic condition was assessed.
Results: Higher HIF-1α, p-Stat3, BAK and survivin expression were measured under hypoxia compared to normoxia in parental MDA-MB-231 cells and its two subsets. Successful knockdown of HIF-1α under hypoxia did not produce any significant effect on the expression of its down-stream proteins, e.g., BAK, MCL-1, survivin, cleaved caspase 3, and cleaved PARP, but gave rise to the expression of p-Stat3 and c-Myc. RU cells converted to RR cells under hypoxia. Unexpectedly, knockdown of HIF-1α under hypoxia increased RU to RR conversion.
Conclusion: Hypoxic condition led to the over-expression of HIF-1α, generation of more tumorigenic and resistant phenotype in MDA-MB-231 cells. Unexpectedly, HIF-1α knockdown under hypoxia resulted in increased conversion of cells to more tumorigenic and resistant phenotype. This may be attributed to the compensating effect of other transcription factors overexpressed following HIF1-α knockdown under hypoxia.

2. Replacement of Threonine with Alanine at Position 94 Amino Acid (T94A) of Rat Liver Fatty Acid Binding Protein by Site-Directed Mutagenesis

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Purpose: Liver fatty acid binding protein (L-FABP) is a cytoplasmic polypeptide that binds long-chain fatty acids, eicosanoids, bile acids, and hypolidemic drugs. The L-FABP T94A is a prevalent and common polymorphic variant. The variant is a single-nucleotide polymorphism that has a threonine in the 94th position being replaced by alanine. The purpose of this study is to mutate and isolate the recombinant rat L-FABP to the T94A variant. Further biological studies will be conducted on the isolated variant to elucidate its biological properties.
Methods: *E. coli* from a previous study conducted by our group was confirmed to contain recombinant pGEX-6p-2/L-FABP by purifying the plasmid DNA and digesting with restriction enzymes *BamH1* and *Xho1*. Site-directed mutagenesis was used to induce a DNA substitution at the 94th position exchanging the threonine for an alanine. DNA sequencing was conducted to confirm the presence and location of the substitution. Recombinant L-FABP T94A was

expressed and purified in *E. coli* using a GST tag system. SDS-PAGE and western blot were conducted to detect the recombinant L-FABP T94A variant.
Results: Gel electrophoresis confirmed that the *E. coli* contained the recombinant pGEX-6p-2/L-FABP. Digestion with restriction enzymes *BamH1* and *Xho1* showed two bands, 4900bp was the pGEX-6p-2 and 418bp was the L-FABP. After site-directed mutagenesis, plasmids were transformed into competent DH5α cells, which were then grown on agar plates. The results indicate that the mutant plasmid was properly transformed. DNA sequencing of original and mutated rat L-FABP showed the substitution of the threonine position 94th was substituted for an alanine in the mutated DNA. SDS-PAGE and western blot confirmed proper purification of L-FABP and L-FABP T94A variant.
Conclusion: Replacement of threonine with alanine at the 94th amino acid (T94A) of rat L-FABP was properly constructed. Original and site-directed mutant rat L-FABP was successfully purified.

3. Tyrosine Kinase Inhibitors Decrease Molecular Biomarkers of Fibrosis in Activated Hepatic Stellate Cells in vitro

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Purpose: Hepatic fibrosis is a worldwide problem threatening human health due to the risk of complications. Hepatic injury stimulates a wound-healing response and continuous injury results in an excessive accumulation of extracellular matrix (ECM), hepatic fibrosis and ultimately cirrhosis or other serious hepatocellular diseases. The Tyrosine Kinase Inhibitors (TKIs) have shown antifibrotic effects and may represent a new generation of antifibrotic drugs. In computational analyses we demonstrated for Ibrutinib and Dabrafenib, two recently approved anticancer TKIs, had more favourable binding energies to PPARγ than the known PPARγ agonist, Rosiglitazone, which also has reported antifibrotic effects in the liver. The nuclear receptor, peroxisome proliferator-associated receptor--γ, is involved in cell proliferation and ECM production. Based on the above observations, we hypothesize that Ibrutinib and Dabrafenib suppress hepatic stellate cell activation via PPARγ agonism.
Methods: To confirm *in silico* results, we purchased a commercially available PPARγ competitive binding assay kit and a Cignal Reporter assay kit to assess Ibrutinib's and Dabrafenib's binding affinity and transactivation potential of PPARγ, respectively, using rosiglitazone as positive control. The HepG2 cell line, which expresses adequate endogenous PPARγ, was used for assessment of transactivation potential. To assess the antifibrotic effects *in vitro*, we determined the expression of fibrosis biomarkers and PPARγ using qPCR in both quiescent and activated human hepatic stellate cells (LX-2) treated with Ibrutinib and Dabrafenib at various concentrations.
Results: The binding EC_{50} values of Ibrutinib and Dabrafenib exceeded solubility limits and 100 μM, respectively. Ibrutinib caused limited transactivation of PPARγ while Dabrafenib failed to transactivate PPARγ in HepG2 cells. Ibrutinib and Dabrafenib decreased the mRNA expression of fibrosis biomarkers in activated LX-2 cells, but not PPARγ.
Conclusion: Based on our study, Ibrutinib and Dabrafenib are poor agonists of PPARγ. Reductions in fibrotic biomarkers suggest possible antifibrotic effects which do not involve the PPARγ pathway.

4. Zirconium-89 Labeled Gene Delivery Nanoparticles as Theranostic Agents for Melanoma

Istvan Hajdu[1], Deborah Michel[1], Mays Al-Dulaymi[1], Waleed Mohammed-Saeid[1], Kishor Wasan[1], Humphrey Fonge[2], Ildiko Badea[1]
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Purpose: The overall approach to use targeted nanoparticles as carriers, for both therapeutic and contrast agents is that drug delivery and efficacy can be monitored simultaneously in a non-invasive manner. The goal of our research was to develop a specific Zirconium-89 (^{89}Zr) -labeled DNA delivery nanosystem and clarify its in vitro and in vivo behavior.
Methods: DNA containing nanoparticles were formulated using peptide-modified gemini lipid and deferoxamine modified gemini lipid. The

nanoparticles were characterized by dynamic light scattering, zeta potential analyzer and wide-angle X-ray scattering and radiolabeled with ^{89}Zr. Radiolabeling efficiency, serum stability, gene expression and cell viability were investigated in A375 human melanoma cells. Biodistribution and pharmacokinetic profile were examined in athymic CD-1 nude mice by gamma counter.

Results: The average hydrodynamic size of the nanoparticles was 114±2 nm and zeta potential +31.6.3±1.4 mV. A high labeling stability of the ^{89}Zr-labeled nanoparticles was observed, and gene expression was similar to the non-labeled formulations. The nanoparticles showed longer plasma half-life ($t_{1/2}$ = 10.1 ± 0.4 h vs. $t_{1/2}$ = 1.3 ± 0.1 h) compared to the lipid alone. As expected, the ^{89}Zr-labeled nanoparticles showed higher liver accumulation (33.87 ± 2.20% ID/g vs 20.75 ± 5.35% ID/g,) and lower kidney accumulation (0.96 ± 0.08% ID/g vs 1.34 ± 0.16% ID/g) of the compared to radiolabeled lipid, which suggests that the nanoparticles remained intact in the blood, and these intact nanoparticles spend sufficient time in the blood stream for a specific tissue accumulation.

Conclusions: The DNA containing radiolabeled delivery system was successfully prepared. The labeled nanoparticles were stable and showed similar in vitro characteristics to the non-labeled nanoparticles. It was established that the intact nanoparticles have significantly different pharmacokinetic and accumulation profile compared to the lipid and show potential for applications in targeted cancer gene therapy.

5. Disparate Effects of Resveratrol and Analogues (Pterostilbene and Gnetol) in the Spontaneously Hypertensive Heart Failure (SHHF) Rat

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Purpose: Significant research interest to date has focused on the polyphenol, resveratrol (trans-3,5,4'-trihydroxystilbene), a stilbenoid that is purportedly linked to improved longevity and cardiovascular health. Although resveratrol is well-tolerated in humans, it is readily metabolized and exhibits low bioavailability. Therefore, we queried whether resveratrol analogues would produce greater vasculoprotective effects in an experimental model of hypertension and heart failure.

Method: Sprague-Dawley (SD) and SHHF rats (n=8) were treated for 8 weeks by gavage with vehicle control (C) or low doses (2.5 mg/kg/d) of resveratrol (R), pterostilbene (P), and gnetol (G). Blood pressure was measured by tail-cuff plethysmography. Animals were anesthetized and third-order mesenteric resistance arteries were isolated. Vascular function, structure and mechanical properties were evaluated by pressure myography.

Results: Systolic blood pressure was increased in the SHHF rat (196±3 mm Hg, vs. SD 142±7 mm Hg, $p<0.01$), and was unaffected by stilbenoid treatment. Lumen diameters were reduced in SHHF vessels (200±5 μm vs. SD 318±9 μm, $p<0.01$). As media cross-sectional area was unchanged, media-to-lumen ratios increased (SHHF 17.4±1.2 vs. SD 8.9±0.5, $p<0.01$); these changes mimic the "eutrophic remodelling" that occurs in resistance arteries from patients with essential hypertension. Lumen narrowing in SHHF arteries was attenuated by resveratrol and pterostilbene (SHHF-R 237±6 μm and SHHF-P 238±6 μm, $p<0.01$), but not gnetol (SHHF-G 223±9 μm), whereas media-to-lumen ratio was reduced toward normal by all three stilbenoids (SHHF-R 13.8±0.8, SHHF-P 13.7±0.5, SHHF-G 13.0±0.3, $p<0.01$).

Conclusion: The mesenteric resistance arteries of the SHHF rat exhibit eutrophic remodeling, modeling small artery disease in human essential hypertension. Resveratrol, pterostilbene, and gnetol failed to lower blood pressure; importantly, this suggests that vascular improvement was not secondary to blood pressure lowering, but rather a result of direct actions on the arterial wall. Thus, further research on stilbenoid polyphenols as an adjunct to current anti-hypertensive therapy is warranted.

6. Characterization of Low Affinity Folate Transporters at the Blood-Brain-Barrier

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Purpose: Folates (vitamin B9) play an important role in tissue development and repair. Three major transport systems exist by which folates enter cells: the proton-coupled folate transporter (PCFT), reduced folate carrier (RFC), and folate receptor alpha (FRα). Of these transporters, FRα binds to folates with the highest affinity (K_M = 1nM) and plays a predominant role in brain folate uptake at the choroid plexus. Mutations to and/or antibodies against FRα can cause severe folate deficiency in the brain and result in early childhood neurodegeneration. We hypothesise that in the context of mutations and/or presence of FRα antibodies that would impair folate uptake at the choroid plexus, the low affinity folate transporters (PCFT and RFC) expressed at the blood-brain barrier (BBB) could play a significant role in brain folate uptake. The aim of this project is to characterize the function of the low affinity folate transporters at the BBB.
Methods: Transport assays were conducted in a human brain microvessel endothelial cell line (hCMEC/D3) representative of the BBB. Uptake of radiolabelled folic acid (^{3}H-FA) was measured at pH 5.5 and 7.4, which reflect the optimal pH of PCFT and RFC, respectively, as well as in the presence of standard PCFT inhibitors (4,4'-diisothiocyano-2,2'-stilbenedisulfonic acid or DIDS, bromosulfophthalein or BSP, and sulfasalazine).
Results: ^{3}H-FA uptake by hCMEC/D3 cells was stimulated by an acidic extracellular pH, with time-dependent uptake being higher at pH 5.5 compared to 7.4. At pH 5.5, ^{3}H-FA uptake was significantly inhibited by DIDS (55%), BSP (45%), and sulfasalazine (40%).
Conclusion: The pH dependency and susceptibility to PCFT inhibitors suggest a potential role for PCFT in folic acid uptake at the BBB. Further work will involve full characterization of PCFT kinetic and energetic properties in hCMEC/D3 cells. Further work will also be conducted to investigate the role of nuclear receptors in regulating folate transporters, particularly PCFT, at the BBB.
Acknowledgement: I am a recipient of the 2016 National Summer Student Research Program Award sponsored by GlaxoSmithKline Inc.

7. Demystifying Molecular and Cellular Mechanisms for Identifying Druggable Targets within Breast Cancer Cell Lines Using Newer Tyrosine Kinase Inhibitors

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Purpose: The human epidermal growth factor receptor (HER), the estrogen receptor (ER), and progesterone receptor (PR) expression, amplification, and the absence of these receptors play a major role in tumor survival. Tyrosine kinases (TKs) govern cancer progression and control. Several small molecule inhibitors of TKs (TKIs) (targeted therapy) have been successfully used clinically. Ibrutinib (Imbruvica^{TM}), an orally administered, irreversible inhibitor marketed as a Bruton's Tyrosine Kinase (BTK) inhibitor for treatment of several B-cell malignancies, has recently shown greater cytotoxicity towards HER2 positive breast cancer (BC) cells. Interestingly, Ibrutinib is not exclusive to BTK. Therefore, we decided to use Ibrutinib as a model drug to evaluate the changes in expression of several protein kinases (PKs) in heterogeneous forms of BC cell lines in order to find translational evidence to support the idea of utilizing Ibrutinib and several other newer TKIs as candidates for the treatment of primary and difficult to treat metastatic breast cancer.
Methods: We plan to identify key targets within HER2 dependent and independent pathways primarily using various *in-vitro* assays (cytotoxicity, mitochondrial activity, and protein and RNA expression).
Results: In a preliminary study by our lab, Ibrutinib caused complete tumor regression in an immunocompromised orthotopic murine model using the M4A4-GFP cell line. The relative cellular cytotoxicity of ibrutinib, evaluated by different assays (primarily: Calcein AM assay) for HER positive (+) cell lines was <100 nM while 5000 - 12,000 nM for ER-PR positive (+), and >15000 nM for ER-PR negative (-) cell lines.
Conclusion: These preliminary results provide evidence for Ibrutinib's interference in HER family mediated pathways within HER2 amplified cells and interference with HER members and other PKs in non-HER2 amplified BC cells.

8. Characterizing the Molecular Signaling Pathways in the Cerebral Arteries of Stroke-prone Spontaneously Hypertensive Rats (SHRsp) Before and After Stroke

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Introduction: A loss of cerebral blood flow autoregulation in stroke-prone spontaneously hypertensive rat (SHRsp) is associated with hemorrhagic stroke. To understand why fatal stroke risk is elevated in patients with inflammatory diseases, we use SHRsp's middle cerebral arteries (MCA) to study the underlying signalling change may be occurring before stroke develops, leading to dysregulation of MCA contraction, which may be responsible for the loss of the ability of the MCAs to autoregulate after stroke.
Methods: MCA samples from SHRsp animals are collected at 9 weeks for pre-stroke and after evidence of stroke (around 15 weeks or more) for post-stroke. The MCAs were either isolated to measure protein levels and expression using western blot or immunofluorescence. Tissues were analyzed for activation of neuro-inflammation, total and activated inflammatory proteins (ERK and MAPK), and proteins involved in cerebrovascular contraction (PKC an MLC).
Results: Preliminary results from IHC indicate activated inflammatory proteins (ERK & MAPK) & neuroinflammatory markers (astrocytes & Microglia) are increased after stroke with an associated decrease in expression of activated protein kinase C(PKC-involved in activating contractile proteins) compared to pre-stroke SHRsps. Preliminary results from western blot shows significantly lower phospho ERK/Total ERK, as well as a significantly lower Phospho MAPK/Total MAPK in post stroke animals in comparison to pre stroke group. Post stroke samples also show significantly lower Total MAPK/GAPDH, but appear to have a significantly higher Total ERK/GAPDH compared to pre stroke. Conversely, post stroke MCAs appear to have a numerically higher phospho PKC/Total PKC when compared to pre stroke.
Conclusion: Overall, it appears that there is an increase in active inflammation and decrease in active PKC (involved in contraction). The consequence of decrease in the ratio of active inflammatory proteins/total remains to be determined.

9. Effects of a Binge Drinking Ethanol Administration Protocol on the Long-term Motor Function and Cerebellar Physiology of Adolescent Rats

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Purpose: Binge drinking among adolescents is a growing 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, after binge drinking.
Methods: Rats of two different ages were used in order to examine the effects of ethanol on adolescent (PND 30) and periadolescent (PND 26) subjects. Behavioral testing consisted of the fixed speed rota-rod (FSRR), accelerating rota-rod (ARR), and cage hang tests designed to assess motor function. After being divided into equal groups of experimental and control, subjects were exposed to either ethanol or plain air through a vapour chamber apparatus for five consecutive days. Blood ethanol concentrations (BECs) were taken on each treatment day after exposure in both groups. Behavioral tests were conducted prior to beginning the ethanol exposure, on each exposure day before being placed into the vapour chamber, and at several other times for the month following treatment.
Results: Results from the FSRR and cage hang testing indicated a significant difference between groups that persisted for up to 30 days after treatment. The ARR testing did not show as strong an effect and it only persisted for approximately one week after treatment.
Conclusion: Additional studies are currently underway and will utilize a number of techniques in order to investigate the biological changes in the cerebellum. These results will allow us to more conclusively state that binge drinking during adolescence can cause significant changes to cerebellar function at the neuronal level.

10. Chemical Analysis and Neurobiological Effects of Newfoundland Wild Blueberries

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[1]School of Pharmacy and [2]Department of Biology, Memorial University of Newfoundland

Purpose: In order to treat some neurological diseases, antioxidants such as polyphenols and ascorbate found in *Vaccinium* berry species may be an effective addition to medicinal products. Polyphenols may reduce oxidative stress and inflammation, processes believed to contribute to degenerative disorders such as Parkinson's disease. We have performed an analysis of the biochemical attributes and neurobiological activity of compounds detected in *Vaccinium* species. In particular, we are investigating the effects of berry extracts on microglia, which are the innate immune cells of the brain.
Methods: Wild blueberries, native to Newfoundland and Labrador (NL), were collected from different locations. Biochemical assays were performed to determine the phenolic content of extracts and antioxidant capacity. Ascorbic acid levels in wild lingonberries and blueberries were also determined. To quantify and identify major anthocyanins in extracts, High-Performance Liquid Chromatography Mass-Spectroscopy (HPLC-MS) analysis was performed. Microglial cells isolated from mouse brains were treated with glutamate or α-synuclein to induce inflammatory responses, and treatment with extracts was conducted in order to assess neuroprotective effects.
Results: Biochemical assays indicated that leaves have a significantly higher content of polyphenols and ascorbate in comparison to fruits. Blueberries had a higher level of ascorbate in both the leaf and fruit extract compared to wild lingonberries. Utilizing HPLC-MS, more anthocyanins were identified in blueberry fruit than leaves, but the anthocyanins present in leaf extracts were present in higher quantity. Cell culture experiments are still ongoing, to determine the potential of berries to inhibit inflammatory responses in the brain.
Conclusion: Wild blueberry fruits and leaves native to NL are high sources of antioxidants, especially phenolic and ascorbate levels. Leaves have an overall significantly higher level of antioxidants compared to the fruits. The results of the cell culture experiments could demonstrate the preventative role that blueberry fruits and leaves have on certain neurodegenerative diseases.

11. Cobalt $^{(III)}$ Complexes as Pro-drugs for Cancer Therapy

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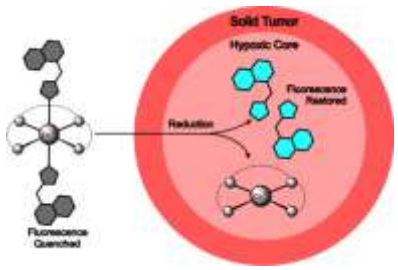
Simon Fraser University, Burnaby, BC

Purpose: Cancer is one of the leading causes of death, and though numerous cancer treatments have been developed, the overall selectivity and effectiveness of treatments need to be improved. Exploiting differences between cancerous tissue and normal tissue has proven successful, and compared to normal tissue, cancerous tissue exhibits uncontrolled growth leading to inefficient blood vessel formation, restricting blood flow and the delivery of drugs and oxygen to the inner regions of tumors. The lack of oxygen, termed hypoxia, results in a reducing environment in tumors. Exploiting the reducing environment of tumors to activate a drug molecule offers a potentially selective treatment strategy. We aim to design pro-drugs that are initially administered to the body in an inactive form, and can be only selectively activated under the reducing conditions found in tumors.
Methods: We synthesized octahedral Co^{III} complexes in which the metal center is coordinated by a tetradentate salen ligand and two axial fluorescent ligands. The fluorescence is quenched while bound to the Co^{III} center, but upon release we can use fluorescence spectroscopy as a proof-of-principle for our design strategy.

Results: Upon reduction of the Co^{III} metal center to Co^{II}, the axial ligands were released from the more kinetically-labile metal centre, and fluorescence release was observed. Salen ligand modification provides a mechanism to tune the reduction potential of complexes for selective release in the reducing environment of tumors.



Conclusion: This methodology can be utilized for Co^{III} complexes as a drug delivery platform for the selective release of axially-bound anticancer agents.

12. Identification of the Mechanism of Action of Chemical Probes Against the Key Autophagy Enzyme ATG4B

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Purpose: Autophagy, the catabolic process responsible for degrading and recycling cellular components, has been implicated in numerous disease states, including neurological disorders and many cancers. Although it has been postulated that inhibition of ATG4B, a key enzyme in autophagy, may allow modulation of these conditions, no chemical probes have been reported to date with which to test this hypothesis. Two chemical probes against ATG4B have been developed in our laborotories; however, with the exception of computational modeling, the binding site for these compounds remains unknown, hindering identification of their mode of action and further optimisation.
Methods: Enzymatic assays of ATG4B can be used to study the kinetics of inhibition of these compounds, giving evidence towards the mode of inhibition. Alternatively, development of photoaffinity probes bearing photolabile groups can be used to irreversibly label the binding site, which can then be identified using peptide digests and the known crystal structure of the enzyme.
Results: Kinetic evidence has been obtained towards the binding mode of the qunioline-based chemical probe, which has been compared to that predicted from *in silico* modeling. Concomitantly, a derivative of the thiazole-based probe has been designed and synthesised featuring a photolabile diazirine group. This photoaffinity probe has a comparable affinity to the parent compound, suggesting the binding mode is unaffected by the introduced group. Labelling studies and protein digests are ongoing to identify the localisation of this compound.
Conclusion: Enzyme kinetics and the development of a photoaffinity probe have lent evidence towards the binding sites of these chemical probes against ATG4B, assisting in both the identification of their mechanism of action and in further optimisation of these ligands.

13. Long-term Adipose Tissue Preservation by Oxygen Delivery

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Purpose: Maintaining adipose tissue viability is very important for the study of metabolic activities of adipose tissue, fat transplants for reconstruction and obesity. We sought to preserve a large volume of adipose tissue under anoxia by encapsulating adipose tissue into an oxygen delivery scaffold and evaluated both cell viability and functionality of the tissue.
Method: Oxygen releasing ~50-200µm microparticles consisting of calcium peroxide (CaO_2) in a polymeric matrix were prepared. For *in vitro* tissue preservation, the effect of oxygen concentration on cell viability was investigated by changing the concentration of microparticles in the scaffold. Adipose tissue encapsulated in alginate only was used as a negative control. The scaffolds were cultured under anoxia for up to 25 d. ELISA was performed to examine necrosis and inflammation related markers, necrosis factor (TNF) and lipocalin-2. Finally adipose tissue transplantation was attempted in cylindrical polymer moulds and the effect of oxygen delivery on tissue necrosis and resorption was determined.
Results: Oxygen supply maintained high cell viability in adipose tissue under anoxia for up to 25 days. Viability of spheres of tissue up to 1cm in diameter could be maintained in anoxia throughout their thickness for up to 7 days. The oxygen preserved adipose tissue secreted a significantly less TNF.
Conclusion: Oxygen delivery successfully prolonged preservation of adipose tissue *in vitro*. This method could be used to build an *ex vivo* models of adipose tissue for pharmaceutical and metabolic studies e.g. in the search for a non-surgical approach to morbid obesity treatment.

Clinical Sciences & Pharmacy Practice

14. Ethnicity and Natural Health Products Usage: Perceptions, Safety, and Pharmacoeconomics

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Purpose: Despite studies looking at immigrant use of NHPs, few have considered economic impacts along with perceptions and attitudes towards such use. The aim of this study was therefore to determine new immigrant patterns of NHP use in order to guide the provision of complete and comprehensive health care to this patient group.
Methods: A survey consisting of 40 questions was completed by new immigrants in the Brampton and Oakville areas of Ontario during English Language Training classes offered in the years of 2012 and 2013.
Results: Almost all participants believed that NHPs can be used for general health in addition to certain conditions; when prompted on whether they believed NHPs can be considered safe, many participants agreed that NHPs are not safe however were unable to provide robust examples of unsafe NHP and medication combinations. From a pharmacoeconomic standpoint, most participants indicated that the price of NHPs was within their budget while the price of prescription medications was not. Perhaps most interesting were the results related to purchases made by new immigrants for short and long term illnesses: a high percentage of participants would purchase the prescription medication for a short term illness over the natural health product; however this percentage decreases in the event of a long term illness, with more participants relying on natural health products to remedy their long term illness symptoms.
Conclusion: The results of this study illustrate that many new immigrants utilize NHPs and rely on such products for short and long term illnesses. The participants appeared not to be able to identify NHP-drug interactions nor appreciate the definition of an adverse event. These results can be used to guide safer clinical practices for new immigrants by educating health care professionals on common perceptions of such products.

15. A Comparative Risk of Cardiovascular Events between Incident SSRI and SNRI Use: A Population-based Study

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Purpose: Selective serotonin reuptake inhibitors (SSRI) and serotonin norepinephrine reuptake inhibitors (SNRI) are widely prescribed for mood and anxiety. SNRIs have been associated with hypertension; however, the clinical significance of SNRIs contributing to cardiovascular events relative to SSRIs is unclear. We aimed to compare the risk of cardiovascular events between the incident use of SSRIs and SNRIs.
Methods: This was a population-based, retrospective cohort study of Manitoba residents using administrative databases from the Manitoba Centre for Health Policy. All patients who started an SSRI or SNRI between April 1, 1998 and March 31, 2014 were included. The primary outcome was a composite of myocardial infarction (MI), stroke, or cardiovascular-related hospitalization within one year of drug initiation. Each component of the primary outcome was analyzed separately in a secondary analysis. Inverse probability of treatment weighting with propensity score was used to account for baseline differences between the two groups.
Results: A total of 225,504 and 54,635 patients initiated treatment on an SSRI and SNRI, respectively. No significant difference was observed for the primary outcome (hazard ratio = 1.01; 95% CI 0.96-1.07), which was experienced by 4467 (2.0%) and 897 (1.7%) in the SSRI and SNRI group, respectively. Secondary analyses also found no differences in the risk of MI or fatal stroke between SSRIs and SNRIs. However, the risk of non-fatal stroke was higher among SNRI users (hazard ratio = 1.11; 95% CI 1.04-1.20), and the risk of cardiovascular-related hospitalization was unexpectedly lower in the SNRI group compared to SSRI users (hazard ratio = 0.87; 95% CI, 0.80-0.95, respectively).
Conclusion: Incident SNRI use was not associated with a higher risk of cardiovascular events relative to

SSRIs. However, further study is warranted for the higher risk of non-fatal stroke and lower risk of cardiovascular-related hospitalization observed among incident SNRI users.

16. A Safety Evaluation of Flaxseed Lignan Supplementation in Healthy Older Adults Following 6 Months of Once Daily Oral Administration

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Purpose: A randomized, double-blind, placebo-controlled clinical trial was designed to further assess the safety and tolerability of a flaxseed lignan complex (~38% secoisolariciresinol diglucoside (SDG)) in elderly healthy populations for 6 months following once daily oral administration. This study was approved through Health Canada (NCT01846117) and U of S Biomedical Research Ethics Board and participants were recruited between 2013 April and 2014 March.
Methods: 32 participants completed the trial after applying all exclusion criteria. Trough blood samples were collected at baseline, 8, 16, and 24 weeks to assess plasma inflammatory markers and plasma flaxseed lignan metabolites. Blood pressure, respiratory rate, pulse, cognition, weight, and height were measured by research staff. Inflammatory markers, IL-6, TNF-α, and C-reactive protein (CRP), were measured using commercially available kits. The plasma levels of flaxseed lignan secoisolariciresinol (SECO), enterodiol (ED), and enterolactone (ENL) were determined using a previously validated LC/MS/MS method. Experimental data were analyzed separately using one-way ANOVA with repeat measures by SPSS (IBM SPSS Statistics 22, NY, US). The treatment to placebo significance was set at p=0.05.
Results: Flaxseed lignan plasma metabolite levels (parent and conjugates) were significantly elevated in participants receiving treatment, compared with placebo group ($p<0.05$). Flaxseed lignan complex administration decreased systolic blood pressure (SBP) to 140±11mmHg vs placebo 154±10 mmHg at 24 weeks in the SBP≥140 mmHg subcategory ($p=0.04$). No significant changes were found in the SBP<140 mmHg subcategory between treatment and placebo groups. With respect to respiratory rate, pulse, IL-6, TNF-α, and CRP, no significant difference was found between treatment and placebo group during the 6-month study. Study participants did not report any significant adverse events associated with flaxseed lignan supplementation.
Conclusion: Our data suggest that long-term flaxseed lignan complex supplementation was well tolerated in healthy, elderly adults.

17. A Systematic Review and Bayesian Network Meta Analysis (NMA) to Indirectly Compare the Efficacy of the Subsequent Entry Biologic (SEB) CT-P13 to REMICADE® (infliximab) in Patients with Crohn's Disease (CD)

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Background: CT-P13, a SEB (or biosimilar) to REMICADE®, was approved by Health Canada (HC) using a structural demonstration of similarity and a reduced package of non-clinical and clinical data. HC did not grant the CD and ulcerative colitis (UC) indications due to unresolved residual uncertainty in the absence of clinical data in IBD. In the interim, observational studies have reported real world experience with use of CT-P13 in IBD. The intent of this study was to use Bayesian NMA methodology to indirectly compare response and remission rates between CT-P13 and REMICADE® in CD using published clinical data.
Methods: A systematic review of major databases was conducted for placebo controlled randomized trials (RCTs) evaluating REMICADE® in CD. A second review was undertaken to identify all published clinical data for CT-P13 in similar patients. To match the CT-P13 single arm study to the REMICADE® NMA, a similarity metric was constructed. The metric is expressed on a scale between 0 and 1. CT-P13 study arms with a metric value of ≤ 0.10 were deemed similar enough to be

added to the REMICADE® NMA.
Results: Three REMICADE® RCTs were identified. CT-P13 data in CD included five single arm uncontrolled studies, evaluating a mix of CD and UC patients, some having prior exposure to REMICADE®. The similarity metric indicated that none of the CT-P13 trials were similar enough to be incorporated into the REMICADE® NMA. Therefore given the available CT-P13 data, the NMA could not generate comparative efficacy estimates with any reliability.
Conclusions: Despite best efforts, a NMA could not be reliably performed to indirectly compare CT-P13 to REMICADE®. Consequently, uncertainty with respect to comparative efficacy between CT-P13 and REMICADE® in CD remains. Until data from RCTs becomes available, comparative safety and efficacy remains undetermined.

Drug Delivery & Pharmaceutical Technology

18. *In vivo* Precipitation of Poorly Soluble Drugs from Lipid Based Formulations

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Purpose: The purpose of this study was to investigate if a poorly soluble model drug danazol precipitated in the GI-tract after administration of a LBF to rats.
Methods: A LBF consisting of Transcutol HP and Kolliphor EL (1:1) was prepared and danazol was added to yield a drug load of 52.4 mg/g (80% of saturation solubility in the LBF). Male Sprague Dawley Rats (300-325 g) were fasted for 18 hours with free access to water and received 250 µL formulation in a single dose via oral gavage, corresponding to approximately 13.1 mg Danazol/rat. Two rats were administered 250 µl LBF without danazol as a control. The rats were euthanized with CO_2 0, 15, 30 and 60 minutes after dosing and their stomach and small intestine was surgically removed. After removal the stomach and intestinal content was collected and centrifuged for 10 min. The supernatant was discarded and the pellet was collected and analyzed by X-ray powder Diffraction (XRPD).
Results: XRPD diffractograms of the stomach and intestinal content of the rats dosed with LBF without danazol, were absent of any crystalline matter. The diffractograms of the stomach content of the rats dosed with LBF containing danazol showed reflections corresponding to those of crystalline danazol, regardless of dosing time. None of the rats showed evidence of crystalline danazol in the intestinal content.
Conclusion: The presence of reflections corresponding to those of danazol in the stomach content of all the rats, regardless of dosing time, indicates that danazol precipitates instantly upon dispersion in the stomach. This was in line with previous *in vitro* lipolysis studies of this LBF, suggesting immediate precipitation of danazol upon dispersion[1]. The absence of crystalline danazol in the intestinal content might be due to no transfer of formulation from stomach to the duodenum, as LBFs have been showed to induce a semi-fed state, delaying gastric emptying . It could, however, also be due to fast absorption of danazol in the duodenum, thus forcing the equilibrium of danazol towards the solubilized state. This study shows that precipitation of poorly soluble drugs *in vivo* actually occurs. It is, however, yet to be confirmed if it affects the bioavailability.

19. Investigation of CD205 Targeted PLGA Nanoparticles to Enhance Antigen Specific Immune responses

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Purpose: Cancer vaccines are designed to work by activating cytotoxic T cells and directing them to recognize and act against specific type of cancer antigen or by inducing the production of antibodies that can recognize cancer cells. The aim of this research is to design a vaccination strategy based on nanoparticulate (NP) drug delivery system.

Method: FDA approved poly-(D, L-lactic-co-glycolide) (PLGA), ovalbumin (OVA, antigen) and monophosphoryl lipid A (MPLA, adjuvant) is utilized to prepare NPs by emulsification solvent evaporation method. The dendritic cell targeting ligand (anti-CD205) was attached to NPs via adsorption and covalently binding method.
Results: Formulations had shown suitable physicochemical properties with 79-93% of cell viability after 72 hours. Structural integrity of OVA in NPs was confirmed through circular dichroism. COOH and ester terminated PLGA NPs released 50% OVA in 24 hours and 7 days, respectively. T cell proliferation study confirmed the proliferation of CD8 T cells for both wild type balb/c and OVA-transgenic-1 (OT-1) mice. Antigen specific immune response was obtained in WT mice treated with ligand (adsorbed) modified OVA-MPLA 0.18 iv COOH NPs. This formulation showed about 93% of dividing populations in different generations. The same formulation secreted the highest amount of IFNγ (12.94 ng/ml), IL-2 (1294.22 pg/ml), TNF-α (4566.21 pg/ml) and IL-6 (1299.66 ng/ml). In contrast, OVA-transgenic mice showed 81.1% of dividing population after re-stimulation with 20 times lower dose of OVA-peptide. The cytokines secreted were IFNγ (25.03 ng/ml), IL-2 (1890.94 pg/ml), IL-6 (1691.62 pg/ml) and TNF-α (3862.19 pg/ml) by covalently modified OVA-MPLA COOH NPs.
Conclusion: In conclusion, the findings confirm that PLGA NPs carrying cancer antigens are able to produce antigen specific immune responses. This response could be generalized to any type of cancer depending on the antigen loaded in NPs, which could be considered a vaccine for a wide range of cancer types.

20. Multi-location Multiple Stimuli-Responsive Degradation: A New Strategy for Accelerated Drug Release and Cancer Therapy

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Purposes: Well-defined amphiphilic block copolymers and their self-assembled nanostructures designed with stimuli-responsive degradation (SRD) have been extensively explored as a choice of promising nanocarriers for pharmaceutical science and cancer therapy. SRD involves the incorporation of dynamic covalent linkages, which can be later cleaved in response to external stimuli, preferably cellular components. Thus, SRD-exhibiting nanocarriers, which are stable under physiological conditions during blood circulation, can be dissociated in a controlled fashion as cellular components provide the appropriate stimuli to trigger biodegradation in microenvironments of tumors and inside cancer cells. Numerous methods have been reported for the synthesis of stimuli-responsive degradable block copolymers and their self-assembled nanostructures. However, most conventional methods incorporate cleavable linkages of different densities positioned at single locations, such as the micellar core or the interface between hydrophobic core and coronas (Single location SRD).
Methods: Our research group has recently focused on an effective SRD strategy that centers on the development of new intracellular nanocarriers having multiple stimuli-responsive cleavable linkages at multiple locations, as in the micellar core, in the interlayered corona, and at the interface between the hydrophobic core and corona (denoted as ML-MSRD strategy). A typical dynamic linkage is a disulfide bond that can be cleaved to corresponding thiols in a reducing environment. In biological systems, the reducing agent glutathione occurs at different concentrations in intracellular versus extracellular environments; importantly, in cancer cells levels are elevated. Other biocompatible stimuli include acidic pH, enzymes, and light.
Results and Conclusions: This new strategy dramatically increases versatility since responses to each stimulus can independently and precisely regulate release of encapsulated biomolecules at several locations. Further, the strategy enables the investigation of structure-property relationship between morphological variance and stimuli-responsive degradation. Ultimately, the results enable the optimization of degradable micelles offering enhanced release inside diseased cells, particularly targeted cancer cells.

21. *In Vitro* and *In Vivo* Characterization of Tabletted Spray-Congealed Lipid Microparticles for Extended Release of Vildagliptin

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Purpose: The spray-congealing (SC) microparticles preparation technique was used to design an extended-release oral tablet for Vildagliptin (VG) to be administered once daily in treatment of type-2 diabetes mellitus.
Methods: Gelucire 50/13 and compritol lipid carriers were heated at 10 ^{o}C above their melting points. VG and Carbomer were dispersed in the lipid molten mass and sprayed through the two fluid nozzle of the Buchi spray-congealer. Produced VG loaded microparticles (MP) were compressed into tablets and further characterized for their morphological characteristics, physicochemical properties, content analysis, *in vitro* dissolution and *in vivo* bioavailability studies using nine mixed-bred dogs in a crossover study design. The quantitative analysis was done using a validated high pressure liquid chromatography with a photodiode array PDA detector for *in vitro* results and mass detector MS was utilized for the *in vivo* VG concentrations.
Results: VG microparticles were amorphous, spherical in shape with a total yield of 76%. The VG content in the microparticles was found to be 98.8%. The *in vitro* dissolution studies showed that VG was released from the tableted particles in a sustained-release fashion for up to 24 hours in comparison to the immediate-release VG marketed tablets, which released the drug within 30 minutes. The release profile of the SC formulation was similar after a storage period of 6 months. The *in vivo* pharmacokinetics studies reported a C_{max}, $T_{max,}$ $T_{1/2}$ and mean residence time of 118 ng/ml, 3.4 h, 5.3 h and 9.8 h respectively for the spray-congealed formulation with a significant difference when compared to those of the immediate-release marketed drug (147ng/ml, 1 h, 2.1 h and 2.8 h respectively). The area under the peak (AUC) of the tested and the reference were not significantly different.
Conclusion: SC technology was successfully utilized for the preparation of extended-release tabletted microparticles for VG.

22. Novel Application of siRNA-PEI Encapsulated Nanoparticles in Preventing Vaginal Infection of Chlamydia Trachomatis via PDGFR- β Knockdown and Autophagy Induction

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Purpose: The aim of this study was to evaluate the novel application of small interfering RNA(siRNA)-polyethylenimine (PEI) encapsulated nanoparticles (NPs) in preventing vaginal infection of chlamydia trachomatis via the knockdown of platelet-derived growth factor- β (PDGFR- β)(an irreversible binding receptor for chlamydia trachomatis and an autophagy-irrelevant gene) and the induction of autophagy.
Methods: siRNA was first condensed by PEI and then co-encapsulated into NPs by double-emulsion evaporation method using the biodegradable polymer, poly(lactic-co-glycolic acid)-polyethylene glycol (PLGA-PEG).
Results: Scramble siRNA-PEI NPs (256.3±7.8 nm) could significantly induce autophagy in vaginal epithelial cells (VK2/E6E7) upon a 48 hr treatment of 1.34 mg/mL NPs (equivalent to 37.6 μg/mL of PEI), evidenced by the increased level of autophagic flux (>6 folds compared to naïve control) and decreased level of LC3-B (>15% decrease compared to naïve control), while the free PEI at the same concentration was unable to do so due to massive cell death. Moreover, free PEI (1 μg/mL; highest concentration that does not elicit cell death) and siRNA NPs without PEI (1.34 mg/mL) were not able to induce autophagy. The gene expression of three autophagy genes involved in early (VPS 34) and late autophagic stages (UVRAG and TECPR-1) were significantly upregulated by 35%, 33% and 32% respectively, upon the induction of autophagy by scramble siRNA-PEI NPs. The siRNA-PEI NPs were rapidly and efficiently taken up by VK2/E6E7 and caused siRNA transfection in 100% cell population in as early as 3 hrs. siRNA-PEI NPs encapsulating siRNA targeting PDGFR- β (1.34 mg/mL) caused more than 60% gene knockdown in VK2/E6E7 without decreasing cell viability or

inducing pre-inflammatory cytokines (TNF-α, IL1-β, IL-6, IL-8).
Conclusions: We have found and evaluated a novel application of siRNA-PEI NPs as a potential strategy in preventing vaginal infection of chlamydia trachomatis. The downregulation of PDGFR- β can help decrease the bacterial binding to vaginal epithelial cells and the induction of autophagy by the NP formulation itself can help eradicate the invaded bacteria from the cells. The two mechanisms may play a synergistic role in the protection against vaginal chlamydia trachomatis infection.

23. Synthesis of a Gemcitabine Prodrug for Remote Loading into Liposomes and Improved Therapeutic Effect

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Purpose: Liposomal nanoparticles can provide an effective way to passively target the drug payload to a tumour and circumvent associated side effects. For such a treatment to be effective a sufficient quantity of drug must be loaded with adequate stability in the aqueous core of the liposome. A remote loading strategy can be used to achieve this, which relies upon the drug being an amphipathic compound possessing an ionizable functional group. Gemcitabine is not a suitable drug for this purpose because it is relatively hydrophilic and has no suitable ionizable moiety. Here we report an innovative approach to actively and stably load gemcitabine into lipid nanoparticles through the formation of a pro-drug.
Method: Gemcitabine was chemically modified to introduce more lipophilicity and a weak base moiety for remote loading. Several derivatives were synthesized and the solubility, stability, cytotoxicity and loading efficiency of these were screened for their potential to be good liposomal remote loading drug candidates.
Results: Two morpholino derivatives of gemcitabine were chosen as the preferred prodrugs for this purpose as they possessed the best loading efficiencies (100% for drug-to-lipid ratio of 0.36 w/w). This is a considerable improvement over a passive loading strategy where typical loading efficiencies are often in the order of ~10-20% for a drug-to-lipid ratio of ~0.01. Liposomes loaded with these two prodrugs showed improved therapeutic effect over free GEM (~2-fold) and saline control (8- to 10-fold) in an s.c. tumour model in vivo.
Conclusion: This work demonstrates how chemical modification to create a prodrug of a known hydrophilic drug can lead to improved loading, stability and drug delivery in vivo.

24. Stable Encapsulation of Poorly Water-Soluble Drugs into Lipid Nanoparticles for Drug Delivery

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Purpose: Poor aqueous solubility has hampered efficient delivery of many drugs. This study is to develop a new remote loading method (Fig.1) that enables efficient and stable loading of poorly water-soluble drugs into lipid nanoparticles (LNPs) to improve drug delivery.
Method: A small amount of DMSO (normally 2-10% vol) was included during the remote loading process to prevent drug precipitation and facilitate the loading of poorly water-soluble drugs (staurosporine (STS), a pan-tyrosine kinase inhibitor or mefloquine (MEF), an antimalarial drug) into the aqueous core of LNPs composed of DSPC/cholesterol (55/45, molar ratio) with an ammonium sulfate gradient. DMSO and un-encapsulated drugs were then removed by dialysis. Both STS-LNPs and MEF-LNPs were characterized by their size, drug-to-lipid ratio, and drug release kinetics. The safety and antitumor efficacy of the STS-LNPs were compared with free STS in a mouse model. The palatability and bioavailability of MEF-LNPs were compared with a standard MEF suspension.
Results: A high drug loading efficiency with a drug-to-lipid ratio of 0.31-0.36 (mol/mol) was achieved for both STS and MEF. Drug molecules of STS and MEF formed nano-aggregates inside the LNPs, and were stably retained inside the LNPs upon storage at 4°C. A 3-fold higher dose of the STS-LNPs was tolerated by BALB/c mice compared with free STS, leading to nearly complete growth inhibition of a multidrug resistant breast tumor, while free STS only exhibited moderate activity. No drug release for MEF-LNPs was observed in the saliva-mimicking medium for >2 h at 37°C, while the drug release is rapid in simulated gastric fluid (>60% in 30 min) and intestinal fluid (>85% in 30 min). The bitter

taste of MEF was completely masked by the LNP formulation, and the MEF-LNPs exhibited comparable bioavailability in mice compared to the standard MEF suspension

Conclusion: This simple and efficient drug loading method produced a stable LNP formulation for delivering poorly water-soluble drugs, including STS and MEF.

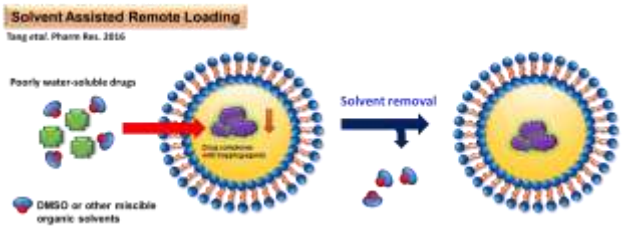

Figure 1. The principle of the solvent-assisted loading technology (SALT)

25. Nanoscale Reaction Vessels Designed for Synthesis of Copper-drug Complexes Suitable for Preclinical Development

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Purpose: Copper-drug complexes (CDCs) are an interesting class of new anticancer agents, some of which appear to be activated in the presence of copper to kill cancer cells. Even though some CDCs are more potent than platinum based cancer drugs (e.g. cisplatin) they have not successfully transitioned into the clinic because of their very poor aqueous solubility. We have developed a method to prepare CDCs inside lipid vesicle (liposomes) whereby the resulting product remains in solution. Copper bis-diethyldithiocarbamate ($Cu(DDC)_2$) was used as a model drug and the synthesis method was successfully demonstrated using other copper-complexing compounds.

Method: Lipid vesicles with encapsulated 300 mM $CuSO_4$ were prepared from phosphatidylcholine (PC) and cholesterol (Chol) (55:45 mole ratio). Using extrusion methods, the diameter of the vesicles was adjusted to ~100 nm. The buffer on the outside of the vesicles was changed to a pH 7.4 buffer and then mixed with selected copper complexing compound. Formation of the copper-drug complexes (CDCs) within the vesicles was measured spectrometrically.

Results: Formation of $Cu(DDC)_2$ inside lipid vesicles was readily detected when DDC was added to the outside of Cu-containing liposomes as the solution colour changed from bluish white to dark brown. The $Cu(DDC)_2$ synthesis reaction occurs in less than 5 min and the stoichometric relationship between Cu^{2+} and DDC inside the liposomes was determined to be 1:2. This approach was used to prepare formulations of Cu-Clioquinol, Cu-Quercetin, and Cu-CX5461 (a targeted drug). Preliminary safety and pharmacokinetic studies in mice demonstrate that the resulting formulations can be administered intravenously. For the $Cu(DDC)_2$ formulation the maximum tolerated dose was 8 mg/kg i.v. Q2Dx14.

Conclusion: Our method provides a simple yet transformative solution enabling, for the first time, the development of CDCs as viable candidate anticancer drugs. These drugs would represent a brand new class of therapeutics for cancer patients.

26. Mechanism of Low Density Lipoprotein Packaged Docosahexaenoic Acid Induced Toxicity of Hepatic Cancer Stem Cells and Mature Cancer Cells

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Purpose: It has been suggested that cancer stem cells (CSCs) within hepatocellular carcinoma (HCC) are responsible for hepatic tumour development and growth. We have successfully isolated and identified CSCs from human Huh-7 and HepG2 HCC cell lines. We then employed the CSCs and residual "mature" cancer cells (MCCs) in experiments designed to document the cytotoxicity and generation of reactive oxygen species (ROS) following exposure to low-density lipoprotein (LDL) packaged docosahexaenoic acid (DHA) (LDL-DHA) nanoparticles, a newly proposed treatment for HCC.

Methods: CSCs and MCCs isolations were achieved by fluorescence-activated cell sorting utilizing

epithelial cell adhesion molecule (EpCAM) and CD133 stem cell markers. Dose- and time-dependent cell cytotoxicity was determined by the WST-1 assay. Cellular ROS levels were evaluated by H_2DCFDA.

Results: Isolated $EpCAM^+CD133^-$ Huh-7 and HepG2 cells (CSCs) exhibited the capacity of self-renewal, tumorigenesis and migration, while $EpCAM^-CD133^-$ (MCCs) failed to do so. After exposure of CSCs and MCCs derived from Huh-7 cells to LDL-DHA nanoparticles, there were dose- and time- dependent effects on cell cytotoxicity. At a concentration of 40μM, LDL-DHA eradicated CSCs and MCCs within 48 hours of exposure. However, LDL-DHA nanoparticles only had a minimal effect on CSCs and MCCs derived from HepG2 cells. After two hours of LDL-DHA exposure, high levels of ROS were detected in CSCs and MCCs from both Huh-7 and HepG2 cells.

Conclusion: In Huh-7 cells, LDL-DHA nanoparticles are equally toxic to both CSCs and MCCs. However, CSCs and MCCs derived from HepG2 cells tend to be resistant to such treatment, despite the induction of similar degrees of oxidative stress.

27. Eutectic Solid Form of Irbesartan-Syringic acid: Mechanistic Evaluation of Thermodynamic Properties, Solid State Characterization and *In Vivo* Studies

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Purpose: Aqueous solubility of BCS II class drugs is the key determinant of their oral bioavailability. Eutectic solid forms (ESFs), in this regard, have gained wide attention among pharmaceutical scientists to overcome this challenge. One of the peculiar properties of ESFs is that they have low melting point owing to depletion in crystal packing energy of binary components resulting in enhanced dissolution rate and thereby improved bioavailability. The aim of present investigation was to prepare ESF of irbesartan (IRB) which is a potent long acting non-peptide angiotensin-II receptor antagonist with low aqueous solubility (< 0.1 mg/mL). Syringic acid (SA) was selected as second component because it belongs to phenolic antioxidant class that exert good cardio-protective effects.

Methods: IRB-syringic acid eutectic solid form (ISA-ESF) was prepared by mechnochemical approach. Initial screening was performed by DSC (differential scanning calorimeter) and PXRD (powder-X ray diffraction) techniques. ISA-ESF was assessed for their physicochemical studies. Antioxidant and *In vivo* antihypertensive activity were investigated in dexamethasone induced hypertensive rats. Pharmacokinetic profile of ISA-ESF was also performed in male Wistar rats.

Results: DSC result of ISA-ESF shows single endothermic event at 162 °C which is lower than both components. Excess enthalpy of fusion of ISA-ESF shows its thermodynamic stability. ISA-ESF exhibited higher aqueous solubility (9 times) and improved intrinsic dissolution rate (2 times) than the pure crystalline IRB. ISA-ESF showed significant reduction in plasma hydrogen peroxide concentration and strongly reduced systolic blood pressure in hypertensive rats as compared to pure drug ($p < 0.01$). *In vivo* pharmacokinetic study also revealed marked improvement in the drug absorption parameters (Cmax, AUC) as compared to free drug suspension.

Conclusion: In nutshell, the present study successfully demonstrated improved biopharmaceutical performance along with antioxidant activity of eutectic solid form of IRB prepared with syringic acid for effective management of hypertension.

28. Microfluidics-Based Manufacture of Size-Tunable Liposomes for the Delivery of Small Molecule Therapeutics

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Purpose: Conventional methods for the production of liposomes are labor-intensive and pose numerous challenges in controlling liposome size, scale-up, and reproducibility. The NanoAssemblr™ microfluidic platform can eliminate user variability and is capable of rapid, reproducible, and scalable manufacture of liposomes. Here, we describe the use of microfluidic mixing to manufacture liposomes of defined size and compositions.

Methods: Liposomes were manufactured using the NanoAssemblr™ bench-top instrument (Precision

NanoSystems, Inc., Vancouver, Canada). Lipids such as POPC, DSPC, Cholesterol, and pegylated-lipid were dissolved in ethanol at varying compositions and concentrations. Liposomes were formed by nanoprecipitation achieved by the rapid and controlled mixing of two-inlet fluid streams containing lipids in ethanol and aqueous buffers, through proprietary staggered herringbone mixing (SHM) apparatus.

Results: Microfluidic mixing enabled the rapid and consistent manufacturing of liposomes having diameters ranging from 25 – 150 nm depending on variables such as aqueous:organic flow rate ratio, and lipid composition. Liposomes consisting of saturated DSPC prepared through microfluidics exhibited a higher size as compared to liposomes prepared using an unsaturated lipid such as POPC at similar aqueous:organic flow rate ratios. Liposomes prepared using microfluidics were similar in size at concentrations ranging from 10 – 75 mg/mL, indicating the ability of the system to show consistent and reproducible results within a certain range of lipid concentrations.

Conclusions: Herein, we have shown the potential of liposomes manufactured using the microfluidic platform to be used as carriers for small molecule therapeutics.

29. Microfluidics-based Manufacture of RNA-Lipid Nanoparticles as Potent Delivery Vectors for Manipulating Gene Expression *In Vitro* and *In Vivo*

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Purpose: Recently, lipid nanoparticles (LNPs) have gained interest as efficient carriers for nucleic acids both *in vitro* and *in vivo*. However, their transition from bench to clinic has been slow due to numerous challenges such as poor reproducibility and scalability. Here, we bridge that gap by describing the robust and scalable manufacture of siRNA-LNPs using the microfluidics-based NanoAssemblr™ platform. We further describe the delivery of PTEN siRNA-LNPs into neurons both *in vitro* and *in vivo*.

Methods: LNPs containing a potent siRNA directed against PTEN were prepared using the NanoAssemblr™ bench-top instrument (Precision NanoSystems, Inc., Vancouver, Canada). PTEN is a clinically relevant gene associated with neural regeneration. The siRNA-LNPs were characterized for their encapsulation efficiency using Ribogreen Assay. *In vitro* studies for PTEN gene knockdown were conducted in primary mixed cortical neuronal cell cultures using qPCR. The efficacy of LNPs was tested *in vivo* following local administration of PTEN siRNA-LNPs in the brain and spinal cord of Sprague Dawley rats.

Results: LNPs manufactured using the microfluidics platform exhibited a small size (~50 nm), low PDI (<0.1), and high PTEN siRNA encapsulation efficiency (>95 %). In primary mixed cortical neuronal cell cultures, LNPs mediated a sustained (>80 %) knockdown in PTEN gene expression at low doses of 100 ng/mL for up to 21 days. Controlled localized injections of PTEN siRNA-LNPs into the motorcortex resulted in significant and sustained knockdown (7 days). Similarly, local administration at the site of spinal cord injury significantly decreased PTEN expression 10 days later.

Conclusions: This study reflects the potential of this delivery vector for use in the screening and validation of new nucleic acid therapeutics in neuroscience.

30. Complete Regression of Xenograft Tumors upon Targeted Delivery of Paclitaxel via Π-Π Stacking Stabilized Polymeric Micelles

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Purpose: Improve the therapeutic index of paclitaxel (PTX) by encapsulation in π-π stacking stabilized micelles formulated without chemical cross-linking or covalent drug attachment for tumor-targeted drug delivery [1].
Methods: PTX-loaded polymeric micelles were prepared by dropwise adding of THF solution containing (methoxy poly(ethylene glycol)-b-(N-(2-benzoyloxypropyl) methacrylamide)) (mPEG-bp(HPMAm-Bz)) polymer and PTX into water followed by evaporation of THF. The physicochemical characteristics of the PTX-loaded micelles were analyzed and effects on tumor cell viability *in vitro* were determined by XTT assays. Pharmacokinetics (PK) and biodistribution (BD) of fluorescent-labeled micelles and model drug after intravenous (iv) administration in tumor-bearing mice were determined using multimodal imaging techniques as well as PTX UPLC analysis. Therapeutic efficacy of the PTX-loaded micelles was determined in two human tumor xenograft models (A431 and MDA-MB-468) in mice.
Results: Micelles ranged between 80-100 nm (PDI <0.15) in size and showed high encapsulation efficiency (> 80%). Inhibition of tumor cell viability induced by PTX-loaded micelles was similar to Taxol®. Multimodal imaging demonstrated closely associated PK/BD of the labeled micelles and model drug as well as substantial tumor accumulation 48h post injection. The half-life of PTX encapsulated in micelles was significantly increased (~8 h) when compared to that of Taxol®. PTX could not be detected 24h post injection in the tumors of mice that received PTX formulated in control micelles or Taxol®. In contrast, high concentration of PTX in tumors (~8 ID%/g) of mice that received PTX-loaded mPEG-bp(HPMAm-Bz) micelles was detected correlating with the results of the imaging study. Repeated injections of PTX-loaded micelles were well tolerated at doses of 15-30 mg/kg. In both tumor xenograft models, treatment with Taxol® (15 mg/kg) had little or no effect on tumor growth, while the PTX-loaded micelles (15-30 mg/kg) induced complete tumor regression.
Conclusions: Polymeric micelles stabilized by π-π stacking interactions are considered to be an attractive platform for improving PTX or other highly hydrophobic drug delivery to tumors and to increase their therapeutic index.
Acknowledgements: This research was supported by the China Scholarship Council, the European Research Council (ERC Starting Grant 309495: NeoNaNo) and the German Research Foundation (DFG: LA 2937/1-2).
References: 1. Shi Y. *et al.* ACS Nano. (2015) 9(4):3740-52.

31. Development of a Stable Liposomal Isotretinoin for Drug Delivery

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Purpose: The aim of this study was to develop a stable liposomal formulation of a water-insoluble drug, isotretinoin (ITT), for efficient and safe drug delivery.
Method: The minimal amount of DMSO, required for complete drug solubilisation, was determined by solubility test (1). The main purpose of incorporating DMSO into this remote loading process is to prevent drug precipitation and facilitate the loading of ITT into the liposomal core. Subsequently, the determined amount of DMSO was added to the preformed DSPC/cholesterol (55/45, molar ratio) liposomes with a calcium formate gradient. DMSO and un-loaded drugs were then removed by spin column. Additional optimization of the liposomal ITT was conducted by varying drug-to-lipid ratio and incubation time. To characterize the liposomal ITT formulation, size, loading efficiency, drug release kinetics (in simulated gastric, intestinal fluid, and saliva), and storage stability were determined.
Results: 5% DMSO in borate buffer (v/v) was required for efficient drug loading, as its presence increased the solubility of ITT (<5 μg/mL in water) significantly by 300-fold. 100% drug encapsulation of ITT in liposomes was achieved at 5% DMSO and a drug-to-lipid ratio of 0.1-0.2 (weight ratio), within 35 min at room temperature. The particle size of the liposomal ITT was ~110 nm (PDI < 0.1). Drug release kinetics study is ongoing and will be finished in April. Storage stability will be monitored for at least 6 months.
Conclusion: An effective and stable ITT encapsulation into liposomes, achieved by the solvent-assisted remote loading, may improve poor drug delivery of ITT.
Reference: 1. Tang WL, Chen WC, Roy A, Undzys

E, Li SD. A Simple and Improved Active Loading Method to Efficiently Encapsulate Staurosporine into Lipid-Based Nanoparticles for Enhanced Therapy of Multidrug Resistant Cancer. Pharm Res. 2016 Jan 12.

32. Intratumoral Penetration by a Nanoparticle of Podophyllotoxin on Tumor Spheroids and In vivo Tumor Models

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Purpose: Poor intratumoral penetration in solid tumors has been one of the major challenges limiting the antitumor efficacy of nanomedicines [1, 2]. We have developed a polysaccharide conjugate nanoparticle system for drug penetration to solid tumors.
Methods: Podophyllotixin (PPT, an anti-tubulin drug) and polyethylene glycol (PEG) were covalently conjugated to acetylated carboxymethyl cellulose (CMC-Ac) via ester linkages [3]. We examined how PPT-to-PEG ratio in the conjugate affected properties of the resulting nanoparticles and compared their penetration in a tumor spheroid system and an s.c. tumor in mice.
Results: The size of the resulting nanoparticles increased with the increased PPT/PEG ratio. The conjugate of a PPT/PEG ratio of 20 yielded 120 nm particles, while 20 nm particles were produced with the conjugate of a PPT/PEG ratio of 2. The drug release rates for the 20, 30 and 120 nm particles were 5%, 2.5% and 1%/day, respectively. The 20 nm particles exhibited 2- to 5-fold enhanced cell killing activity and 5- to 20-fold increased delivery to an s.c. tumor compared to the 30 nm and 120 nm particles. In tumor spheroids, the tumor penetration efficiency of the nanoparticles followed the order of 20 nm > 30 nm > 120 nm. The 20 nm particles penetrated the EMT6 tumor spheroids thoroughly in 3 h, while the 120 nm particles displayed little penetration. The in vivo data were consistent with the spheroid data: within the s.c. tumor, >90% of the 20 nm particles penetrated to the hypovascular core, while the larger particles were largely restricted in the hypervascular periphery.
Conclusion: By varying the PPT/PEG ratio in the conjugates, nanoparticles with different physicochemical properties could be prepared. The 20 nm particles displayed significantly enhanced tumor penetration compared to the larger counterparts.
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33. Development of a Segmented Intravaginal Ring for the Combination Delivery of Hydroxychloroquine and siRNA-encapsulated Nanoparticles as a Novel Strategy for Preventing HIV Infection

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Purpose: We developed and characterized a segmented intravaginal ring (IVR) capable of delivering two different compounds. The first segment is coated with a pH-sensitive polymer containing small interfering RNA (siRNA)-loaded nanoparticles. The siRNA-loaded nanoparticles (siRNA-NP) will be released only when the pH of the female genital tract increases to greater than pH 6.5 due to the presence of seminal fluid. The second segment contains hydroxychloroquine (HCQ), an immuno-modulatory drug that will be released in a sustained and controlled manner.
Methods: Poly(lactic-co-glycolic acid)-polyethylene glycol (PLGA-PEG) was used to encapsulate siRNA using the double emulsion method to form nanoparticles (siRNA-NP). siRNA-NP was mixed with a pH-sensitive polymer (Eudragit L100) dissolved in isopropanol, and used to coat a matrix-type IVR segment, fabricated by injection molding from polyurethane. A release study was performed in vaginal fluid simulant at basic and acidic pH. HCQ was loaded in a reservoir-type IVR segment and an in vitro release study was performed in sodium acetate buffer (pH 4.2). The biocompatibility of the IVR segments was evaluated on vaginal epithelial cell lines VK2/E6E7 and ECT1/E6E7 and on vaginal flora *Lactobacillus crispatus* and *jensenii*.
Results: IVR segments coated with a pH-sensitive polymer rapidly released siRNA-NP at pH8.2 but not at pH 4.2. 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). Cytotoxicity evaluation of IVR segments on vaginal cells and lactobacilli demonstrated no changes in cell viability or bacteria growth, respectively.
Conclusion: We developed and characterized a segmented IVR that can deliver HCQ over 21 days and rapidly released siRNA-NP only at pH 8.2. The IVR segments are non-cytotoxic towards vaginal and bacterial cells.

34. Topical Nanoformulation for the Combination Delivery of Peptides for Accelerated Wound Healing and Synergistic Antibacterial Activity

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Introduction: Chronic wounds (CWs) are a serious health care concern as they fail to resolve and are characterized by "non-resolving" chronic inflammatory state. Most current therapies target only single aspect of the CW process making it difficult to achieve effective healing hence, a new paradigm towards development of combination therapies for CWs is urgently required. Serpin A1 is a powerful anti-inflammatory and immunomodulatory agent in CW healing. LL37 is a host defense peptide possessing anti-infective and wound healing properties. Thus, the combination delivery of these peptides (LL37-A1) using solid lipid nanoparticles (SLNs) may potentially accelerate wound healing as well as demonstrate synergistic antibacterial activity.
Objective: To evaluate LL37-A1-SLNs as a potential combination strategy for accelerated wound healing and synergistic antibacterial properties.
Methods: SLNs encapsulated with LL37-A1 were fabricated using solvent-diffusion double emulsion technique. *In vitro* release and *ex vivo* permeation studies were performed in artificial wound fluid pH 7.4. Synergy was evaluated against *S. aureus* and *E. coli* using the Chou-Talalay method. The WH property was investigated in murine Balb/c mice model over a period of 13 days and % wound closure was determined. Histological assessment was performed in order to determine the predominant stages, extent of collagen deposition and formation of blood vessels during the healing process.
Results: *In vitro* release and *ex vivo* permeation of LL37-A1-SLNs followed a biphasic pattern with an intial release of >10% by day 1. Precise combination ratios exhibiting synergy against *S. aureus* and *E. coli* were determined. LL37-A1-SLNs demonstrated faster WH by day 13 with better granulation tissue formation, denser and compact collagen deposition and higher endothelial cell colonization in comparison to controls or individual treated groups.
Conclusion: This is the first study to develop a nanoparticle formulation for the combination delivery of LL37 and A1 as strategy for the treatment of CWs.

35. Poly (oligoethylene glycol methacrylate)-block-poly (D, L-lactide)-based Nanoparticles as Versatile Hydrophobic Drug Delivery Vehicles

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Introduction: Polymeric nanoparticle (NP) drug delivery systems, particularly NPs formulated from the block copolymer poly (ethylene glycol)-*b*-poly (lactic acid) (PEG-*b*-PLA) have shown great clinical potential given their high biocompatibility and degradability. However, the single end functional group on PEG poses limitations on the use of these materials for emerging ligand-receptor targeting systems. Herein, we address this limitation by replacing the PEG block with poly (ethylene glycol methacrylate) (POEGMA) that has a methacrylate backbone and PEG side-chains. POEGMA has been shown to have similar physical and biological properties to PEG but can be copolymerized, enabling facile multi-ligand grafting. In addition, POEGMA can be engineered to be a "smart" polymer for drug delivery, exhibiting a lower critical solution temperature (LCST) by changing the length of the oligoethylene glycol side chains, enabling potential microenvironment-responsive NP delivery.
Methods: Fluorescently labeled **(Cy5)** PLA-*b*-P[OEGMA-*co*-M$(EO)_2$MA] block copolymers were prepared using PLA-Br as a macroinitiator for *atom transfer radical polymerization* of the OEGMA comonomers. Doxorubicin (DOX)-loaded NPs were prepared by solvent exchange and characterized with dynamic light scattering and transmission electron microscopy. Drug loading and release kinetics were

tracked using UV/vis spectrophotometry. NP uptake into MCA205 tumor cells was assayed via confocal microscopy.

Results: The block copolymers exhibited narrow molecular weight distributions (PDI <1.13) and well-defined compositions. The resulting self-assembled NPs were ~50 nm in size and exhibited a well-defined LCST. NPs were loaded with DOX with high encapsulation efficiencies (72%) and enabled prolonged drug release kinetics. PLA-*b*-P[OEGMA-*co*-M$(EO)_2$MA] NPs did not show significant cytotoxicity via an MTT assay-based *in vitro* cell assay. *In vitro* studies to investigate the cell uptake of the NPs are underway and will be reported.

Conclusion: PLA-*b*-P[OEGMA-*co*-M$(EO)_2$MA]-based NPs offer a more versatile delivery platform compared to conventional PEG-PLA NPs with the potential to enable environmentally-responsive targeting and drug release.

36. Polymeric Micelles for Targeted Delivery of Diclofenac and its Ethyl Ester Derivative in Inflammation

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Purpose: Inflammatory conditions such as arthritis cause cardiovascular (CV) complications. Ironically, nonsteroidal anti-inflammatory drugs (NSAID)s that are given to treat inflammation, can cause CV complications upon long term use, as well. Previous studies show high drug distribution to organs such as heart and kidney can play a role in the emergence of CV side effects by NSAIDs. The aim of this study is to develop a polymeric micellar formulation to limit distribution into heart and kidneys of diclofenac (DFN), an NSAID with known CV toxicity. Such formulation is expected to reduce CV side effects of DFN.

Methods: DFN and diclofenac ethyl ester (DFEE) were encapsulated in polymeric micelles prepared from several block copolymers based on methoxy poly(ethylene oxide)-poly(ester)s (PEO-poly(ester)s. Prepared micelles were characterized for their particle size, polydispersity, encapsulation efficiency, drug loading content, and *in-vitro* drug release. The kinetics of enzymatic hydrolysis for DFEE micelles versus free DFEE was, then, examined at 37±0.5° C in rat plasma.

Results: The DFN and DFEE loaded polymeric micelles exhibited particle size in the range of 27.9-50.3 nm and narrow size distribution. The slowest release for DFN micelles was achieved with micelles of PEO-block-poly(α-carboxyl-ε-caprolactone) with a side chain of N,N-dimethyldipropylenetriamine which showed 71±3.2% drug release in 4 h followed by a sustained drug release reaching 100% within 24 h. The DFEE micelles showed slower release in comparison to DFN, and the optimal results were achieved with PEO-poly(ε-caprolactone) micelles with percent release of 6.8±4.7% of the drug in 4 h and 10.8±2.9% in 24 h. Incubation with plasma of polymeric micellar DFEE for 48 h revealed slow appearance of DFN as compared to that with the free DFEE and a good correlation with *in vitro* DFEE release data.

Conclusion: The results show a great potential for polymeric micelles in passive targeting of DFEE in inflammation.

37. Modification of Polymeric Micellar siRNA Delivery Systems with Breast Tumor Selective Peptide Ligands: Towards Development of Breast Tumor Targeted siRNA Nano-delivery Systems

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Purpose: The long term objective of this study is to develop tumor targeted siRNA delivery systems. Here, we explored development of polymeric micellar systems for siRNA delivery modifying their surface with an engineered peptide, P18-4, which has shown high stability in biological fluids and selectivity for breast cancer over normal cells in previous studies.

Methods: Poly(ethylene oxide)-b-poly(α-carboxyl-ε-caprolactone) (PEO-PCCL) and acetal-PEO-PCCL were synthesized and used to conjugate (through their pendent carboxyl groups) spermine (SP) or N,N-dimethyldipropylenetriamine (DP) producing PEO-P(CL-SP), PEO-P(CL-DP) and acetal-PEO-P(CL-DP) block copolymers. A 2:1:1 (w/w) of the above polymers was used to prepare polymeric

micelles for P18-4 conjugation through Schiff base reaction. Using gel electrophoresis, siRNA binding and serum stability in the presence of FBS was tested at different siRNA:polymer ratios for plain versus P18-4 modified micelles. siRNA release as a function of increasing heparin concentration was also examined using 1:16 siRNA: polymer ratio. MDA-MB-435 cells were treated with 300 nM MCL-1 siRNA in a siRNA: polymer ratio of 1:8 and MCL-1 mRNA expression was measured by RT-PCR.

Results: Complete siRNA binding was achieved at siRNA:polymer ratio of 1:8 for both plain and P18-4 modified micelles. At lower siRNA:polymer ratios siRNA binding was less, but still no significant difference in siRNA binding was observed between plain and p18-4 modified micelles. However, siRNA dissociation from P18-4 micelles demanded a smaller concentration of heparin. At siRNA:polymer ratio of ≥ 1:8, around 100% of siRNA was protected against degradation in serum. There was no significant difference between plain and peptide modified micelles in terms of siRNA stabilization either. Plain and P18-4 modified polymeric micellar complexes of MCL-1 siRNA down-regulated the expression of MCL-1 mRNA by 75 and 82%, respectively, compared to their scrambled siRNA controls.

Conclusion: The results point to a potential for P18-4 nano-micelles in siRNA delivery.

38. The Effect of MCL-1 Down Regulation on the Sensitization of Breast Cancer Cells to Doxorubicin and Caelyx®

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Purpose: Increased expression of anti-apoptotic proteins is an important cellular mechanism against chemotherapy effectiveness in cancer. Myeloid cell leukemia 1 (MCL-1) is one of the most up-regulated proteins in doxorubicin-resistant breast cancer cell lines. The objective of this study was to investigate whether MCL-1 down regulation affects doxorubicin treatment in breast cancer cells.

Methods: MDA-MB-435 and MDA-MB-231 cells were exposed to 50 nM MCL-1 siRNA for 48h using lipofectamine as transfecting agent. RT-PCR was used to quantify MCL-1 mRNA expression using GAPDH as housekeeping gene. MTT assay was used to determine cytotoxicity. Both cells were also exposed to different concentration of free or liposomal DOX (Caelyx®) alone, for 24-48h and investigated for their viability by MTT assay. Finally, cells were pretreated with MCL-1 siRNA for 48h; and then treated with doxorubicin or Caelyx® for an additional 24h. Viability of cells following combination treatment was compared to DOX or siRNA monotherapies.

Results: Free DOX presented a lower IC_{50} in breast cancer cells compared to the liposomal DOX, because of the instant availability of free DOX for cell uptake compared to controlled release of DOX and its slower cellular uptake as part of liposomal formulation. MDA-MB-435 cells were more sensitive to DOX treatment compared to MDA-MB-231 cells evidenced by ~ 40 times lower IC_{50} of DOX in these cells. Treatment with MCL-1 siRNA reduced the MCL-1 mRNA expression by ~ 60 % in both cell lines, but did not affect cell viability as monotherapy. MDA-MB-231 cell viability in the presence of DOX was not significantly affected by MCL-1 silencing. However, MCL-1 siRNA pre-treatment made MDA-MB-435 cells more sensitive to free and liposomal DOX.

Conclusions: The effect of MCL-1 down-regulation on the sensitization of breast cancer cells to doxorubicin and Caelyx® is cell dependent.

39. STK-01 a Novel Intravesical Therapy for Non-muscle Invasive Bladder Cancer

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Purpose: Development of novel therapeutics for patients with high-risk non-muscle-invasive bladder cancer is an important topic considering the rather limited options currently available. We have developed a functionalized nanoparticle formulation of docetaxel to improve treatment outcomes of intravesical chemotherapy. Our novel docetaxel formulation is based on hyperbranched polyglycerol (HPG) technology and has shown promising

efficacy in treating non-muscle invasive bladder tumors in mouse xenograft models. The objective of this study was to investigate the effect of intravesical dwell-time with STK-01 in an orthotopic non-muscle invasive bladder cancer model.
Methods: KU7 cells that stably express firefly luciferase (KU7-luc) were inoculated in female nude mice by intravesical instillation and quantified using bioluminescence imaging. Mice with established KU7-luc bladder tumors were given a single intravesical instillation with STK-01 (0.2 mg/ml docetaxel HPG-NH2 formulation) with a dwell of 15, 30, or 60 min. Control mice were catheterized only without instillation. Tumor growth was monitored by bioluminescence and ultrasound imaging techniques.
Results: STK-01 significantly inhibited tumor growth against KU7-luc orthotopic bladder cancer xenografts in a dwell-time dependent manner. A single intravesical therapy with STK-01 for 60 min showed a near complete tumor inhibition in mice.
Conclusion: STK-01 was found to be safe and effective in treating non-muscle invasive bladder tumors in mice. Our data show promising *in vivo* antitumor efficacy and provide preclinical proof-of-principle for the intravesical therapy with STK-01.

Pharmaceutical & Analytical Chemistry

40. Simultaneous Determination of Oxybenzone, Octocrylene, Avobenzone, Octinoxate, Homosalate and Octisalate in Human Sunscreen Lotion by High-performance Liquid Chromatography with Ultraviolet Detection

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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 lipstick, makeup, and lotions contain one or more sunscreen compounds 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 simultaneous determination of Oxybenzone, Octocrylene, Avobenzone Octinoxate, Homosalate and Octisalate in human Sunscreen Lotion by high-performance liquid chromatography.
Method: Methanol was added to sunscreen lotion samples containing Oxybenzone, Octocrylene, Octinoxate, Avobenzone, Homosalate and Octisalate and agitated the sample until dissolved. After dilution, filtered the sample preparation through 0.45 um nylon filter and injected for analysis by high-performance liquid chromatography. Separation was achieved on a Zorbax SB-C18 (250 mm x 4.6 mm, 5 um) analytical column with a mobile phase of 80:20 methanol:water. Detection was at 320 nm using an ultraviolet detector. The mean retention times of Oxybenzone, Octocrylene, Avobenzone, Octinoxate, *cis*-Homosalate, Octisalate and *trans*-Homosalate were 5.4, 19.4, 23.4, 25.1, 27.7, 30.7 and 34.1 min, respectively. Peak areas were fit to a least squares linear regression algorithm.
Results: The method produces acceptable linearity (r^2= more than 0.999 for all analytes) precision (CV= less than 2% for all analytes) and accuracy (recovery= 100$\pm$2.0% for all analytes) to a minimum concentration of 1.0 micrograms per ml in human sunscreen lotion.
Conclusion: The method is very simple, rugged, and convenient. It can be used to analyze six sunscreens in human lotion in a single run with no observable matrix interferences.

41. Histone Lysine Methyltransferase Inhibitors Decrease HOXA9 Expression and Induce Global Changes in Histone Post-translational Modifications

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Purpose: Histone lysine methyltransferase (HKMT) inhibitors are emerging as treatment strategies for mixed lineage leukemia by decreasing expression of the homeobox A9 (HOXA9) oncogene by modulating the methylation status of histones. Since HKMTs are found in all gene promoters, HKMT inhibitors likely alter the expression of many genes. We have observed similar issues with histone deacetlyase inhibitors. We hypothesize that HKMT inhibition will result in changes to unrelated

epigenetic modifications and alter expression of off-target genes.
Methods: Using LC-MS/MS we measured histone modifications in MOLM13 cells over-expressing HOXA9 treated with HKMT inhibitors EPZ4777, EPZ5676 and BRD4770. Changes in HOXA9 expression were measured using the Viia7 qPCR with predesigned TaqMan primers and probes. Histones were isolated with the EpiQuik histone isolation kit (Epigentek) and mRNA isolated with the Purelink RNA purification kit.
Results: HKMT inhibitors of the human disruptor of telomeric silencing 1-like (DOT1L), EPZ5676 and EPZ4777, are expected to decrease HOXA9 expression by inhibiting H3K79 methylation, but treatment resulted in off-target increases in acetyllysine (26.7±8.1% increase), dimethyllysine (24.7±10.5% increase) and symmetric dimethyl arginine (25.3±2.8% increase), as well as decreases in monomethyllysine (4.6±0.6% reduction), trimethyllysine (21.4±1.7% reduction) and asymmetric dimethylarginine (26.5±7.2% reduction). The G9a methyltransferase inhibitor, BRD4770, is expected to decrease H3K9 and H3K27 methylation and have no effect on HOXA9 expression, but shows global decreases in acetyllysine (41.2±9.2% reduction) and monomethyllysine (16.1±5.9% reduction), increases in dimethyllysine (11.5±6.1% increase) and trimethyllysine (37.1±8.4% increase) and substantial increases in total arginine methylation (90.2±13.9% increase). As expected, both inhibitors of DOT1L, EPZ5676 and EPZ4777, inhibit HOXA9 expression in mixed lineage leukemia cell line MOLM13 by qPCR (74.3±0.8% and 38.1±5.3%) reduction respectively). Unexpectedly, BRD4770 also inhibited the expression of HOXA9 (47.9±1.2% reduction).
Conclusion: These results demonstrate that HKMT inhibition can result in unpredictable changes in histone modifications that lead to unpredictable changes in gene expression.

42. Synthesis of Poly(ADP-ribose) Polymerase (PARP) Inhibitors (Phenanthridinones): The Application of Flow Chemistry Techniques in Medicinal Chemistry Programs

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Purpose: Phenanthridinones are one class of poly(ADP-ribose) polymerase (PARP) inhibitors that have shown anti-cancer effects, and are typically synthesized using inefficient batch cross-coupling reactions. Flow chemistry has shown its benefits in performing chemical reactions efficiently and scaling up easily for industrial purpose without modifying reaction conditions. For the enhancement of the drug discovery process, we found the possibility to produce phenanthridinones with photocyclization method under continuous flow conditions in a superior fashion to analogous batch chemistry methods. The aim of this study was to develop a flow-photocyclization method to synthesize phenanthridinones and demonstrate the robustness and scaling-up ability of the method.
Method: A Vapourtec® E2+/E4 flow chemistry system equipped with a UV-150 photochemical reactor was used to perform single-step flow photocyclization reactions, starting from 2-chloro-N-phenylbenzamides.The residence time (reacting time) for the single-step reaction was 50 minutes. The same flow chemistry system equipped with a high temperature tube reactor and a UV-150 photochemical reactor was used to perform two-step flow photocyclization reactions, starting from 2-chlorobenzoyl chlorides and anilines. The residence time for the two-step reaction was 100 minutes including 50 minutes for amide formation and 50 minutes for photocyclization. The products were separated by CombiFlash® RF and the purity was measured by HPLC.
Result: We have obtained a series of phenanthridinones with different substituents. The yields of most single-step flow photocyclization reactions were 67% ~ 99%. The yields of two-step flow photocyclization reactions were 47% ~ 77%. The purities of phenanthridinones were greater than 95%. The reactions can be scaled up without changing reaction conditions, while the yields meet the requirements for industrial processes.
Conclusion: We have developed a highly efficient, robust and environmentally-friendly method to prepare phenanthridinones and its analogues, which will be applied to the development of phenanthridinone-type PARP inhibitors and further our drug discovery efforts.

43. Testicular Cytochrome P450 (CYP) Enzyme Expression Suppression by Phytoestrogen in Adult Male Rats

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Purpose: Genistein, a phytoestrogen and isoflavone, produces many biological effects in mammalian cells, including inhibition of tyrosine kinase and topoisomerase II and antioxidant activity. In humans, the major route of exposure is through consumption of soy beans and soy-based food products. The aim of this study was to investigate on the effect of genistein on the testicular CYP enzyme expression levels.
Method: Adult male Sprague-Dawley rats were randomized into five treatment groups with 6 rats per group. Rats received daily subcutaneous injections of genistein at 4, 40 or 400 µmol/kg, or estradiol benzoate at 0.4 µmol/kg, or vehicle at 1 ml/kg, for 2 weeks. One day after the last treatment, rats were killed and their liver and testes were immediately excised. Testicular microsomes were prepared from individual rats and expression of CYP1B1, CYP2A1, CYP17A1, microsomal epoxide hydrolase (mEH), CYP oxidoreductase (POR) and 3β-hydroxysteroid dehydrogenase (HSD3β) was analyzed by immunoblots. 5 µm-thick cryosections of testis were prepared for immunohistochemical analysis and its morphology was examined.
Result: Testicular protein levels of CYP2A1 and mEH were decreased by 72% and 54%, respectively, for rats treated with genistein at the highest dosage, and by 93% and 74%, respectively, for rats treated with estradiol benzoate compared with the vehicle-treated group. Similarly, treatment with genistein or estradiol decreased testicular CYP17A1 and POR expression. Estradiol or genistein treatment did not change protein levels of HSD3β. No morphological changes in testicular tissue were seen regardless of treatment group.
Conclusion: These findings indicate that genistein at high doses can suppress testicular CYP enzyme expression in adult male rats.
*Part of this work has been presented at Society of Toxicology Annual Meeting on March 15th in the form of a poster presentation.

44. In Vitro Bioactivation of Cyclic Phenol Phosphate Analogues as Potential Inhibitors of Autotaxin

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Purpose: Autotaxin (ATX) is a member of the nucleotide pyrophosphatase/phosphodiesterase family of ectoenzymes. ATX has lysophospholipase D activity that catalyzes the hydrolysis of lysophosphatidylcholine (LPC) into lysophosphatidic acid (LPA) and choline. LPA is a bioactive lipid mediator, which mediates many physiological and pathological processes including, cell survival, proliferation, and migration. This ATX/LPA signalling has been involved in a number of human diseases including cancer. Because most LPA is produced by ATX activity, an inhibitor of ATX would block subsequent LPA signalling. Therefore ATX has become an attractive drug target for developing new anti-cancer therapies. Our objective is to prepare and assess a series of novel cyclic phenol phosphate analogues for their ability to function as irreversible ATX inhibitors in vitro.
Methods: Here we report (i) The development of synthetic methodologies for the preparation of a series of cyclic phenol phosphate analogues as potential inhibitors of ATX; (ii) An assessment of the aqueous stability of these analogues over 6h in 50 mM TRIS buffer at 37°C and pH 8.0 and analysis by high performance liquid chromatography (HPLC) with UV detection; (iii) Determination of the ability of these compounds to inactivate ATX in vitro. This will be performed by ATX inhibition assays, which will be carried out by our colleagues at the University of Memphis.
Results: We successfully synthesized two model analogues A1 and A2 through a multi-step synthetic procedure. Both compounds were determined to be stable at pH 8.0 and 37°C over 6 h.
Conclusion: The proposed cyclic phenol phosphates have not been previously prepared and can thus represent a new orientation for the development of new anti cancer therapies.

Pharmacokinetics & Pharmacodynamics

45. Tetrahydrocurcumin: Pharmacology and Bioavialability and Differential Pharmacological Effects of Curcumin Anologues

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Purpose: To develop a bioanalytical assay to quantify THC, to characterize its bioavailability in rats after (PO) administration, and to identify its pharmacological activities compared to other curcumin analogues.
Methods: An isocratic UHPLC/MS/MS method was developed using a Waters Acquity UPLC BEH C18 column at a flow rate of 0.4ml/min. THC and the internal standard (curcumin) was monitored in MRM positive mode at m/z 373.3>137.1 and m/z 369.3>177.1, respectively. The mobile phase was 45% aqueous acetonitrile in 0.1% formic acid. For the pharmacokinetic study THC was administered by oral gavage to male CD (Sprague-Dawley) rats (500 mg/kg) (n=3). Serum and urine samples were collected up to 72 h post-dose. In vitro anti-oxidant activity, Histone deactylase activity (HDAC), histone acetyltransferase (HAT), anti-inflammatory activity (cyclooxygenase and lipoxygenase inhibition), and cytochrome P450 inhibitory activities of THC were examined using commercial assay kits. In vitro cell viability, and immune activation markers of cytokine / chemokine production were examined by enzyme-linked immunosorbent assays (ELISA) in SupT1 cells.
Results: THC was poorly absorbed orally and was detected in serum and urine exclusively as glucoroconjugates in a 2:1 keto:enol ratio. THC exhibited multiple pharmacological effects in *in vitro* activity screens when compared to curcumin and another analogue (Calebin A). Anti-oxidant activity was as potent as curcumin and Calebin A and was concentration dependent. THC demonstrated concentration dependent inhibition of CYP3A4 and lipoxygenase and cyclooxygenase inhibition whereas this dual activity was not present in curcumin and calebin A. THC did not inhibit HDAC while this activity was demonstrated for other curcumins.
Conclusions: A sensitive, accurate and reproducible analytical method was developed and employed to characterize the pharmacokinetic profile of THC. An unoptimised formulation of THC showed limited oral bioavailability but was detectable in serum and urine as glucuronides. THC exhibited a variety of pharmacological activities.

46. Toxicity and Mechanisms of Transport of a Novel Organometallic Au(III) Compound Compared to Cisplatin on Rat Kidney Tissue Slices ex vivo

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Purpose: The Pt(II) compound cisplatin is widely used as chemotherapeutic agent in cancer treatment. Unfortunately, there is still a lack of knowledge about its mechanisms of accumulation in vitro and ex vivo. So far, the organic cation transporter 2 (OCT2) and copper transporter 1 (CTR1) are assumed to be involved in the accumulation of anticancer platinum drugs. We recently reported on a new series of gold(III)cyclometallated compounds, among which the most active in cancer cells was compound [Au(pyb-H)L1L2]n+ (pyb-H = C^N cyclometallated 2-benzylpyridine, L1 = 1,3,5 triazaphosphaadamantane, L2 = chlorido) (Figure 1). The aim of this study is to evaluate the toxicity and the mechanisms of transport of cisplatin and gold(III) complex.

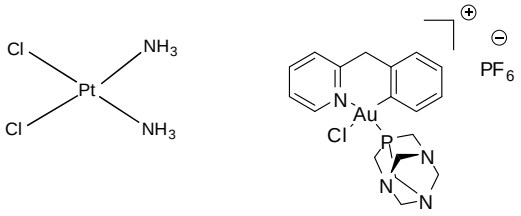

Figure 1: Cisplatin and Au(III) compound

Methods: The mechanisms of accumulation of a cytotoxic cyclometallated gold(III) compound compared to cisplatin are studied on an ex vivo model of precision cut kidney slices (PCKS). The main focus is the evaluation of the effect of cimetidine, an inhibitor for OCT2, on metal compound treated rat kidney slices. Viability was assessed by measuring ATP per protein content. Metal content was evaluated using ICP-MS. Each experiment was performed in triplicates for each condition.
Results: Our results show a correlation between the viability of treated kidney samples and the metal content measured by ICP-MS in differents sets of experiments (incubation times, temperature dependency and +/- OCT2 inhibitor). Moreover, we confirmed the influence of OCT2 on cisplatin accumulation, whereas Au(III)compound showed opposite effects.
Conclusion: Overall, the ex vivo model of PCKS represents a valuable further methodological development in the biological evaluation of metallodrugs.

47. Pre-clinical Pharmacokinetic and Pharmacological Characterization of Liquiritigenin, a Chiral Flavonoid

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Purpose: Liquiritigenin is a chiral flavonoid present in plant based food, nutraceuticals, and traditional medicines. It is also an important ingredient present in licorice. The purpose of this study is to characterize for the first time the stereoselective pharmacokinetics of liquiritigenin after oral and intravenous administration and its pharmacological activity in several *in vitro* assays with relevant roles in colon cancer, and diabetes etiology and pathophysiology.
Methods: Racemic liquiritigenin was intravenously (20 mg/kg) (n=4) and orally (50 mg/kg) (n=4) administered to male Sprague-Dawley rats. Concentrations in serum and urine were collected up to 72 hours after dosing and characterized via stereospecific HPLC. Pure enantiomeric forms were tested to identify the stereospecific contribution to of α-alpha-amylase activity in comparison to the racemate. In-vitro anti-oxidant, anti-cancer, anti-inflammatory activity (cyclooxygenase inhibition), and cytochrome P450 (CYP450) inhibitory activities of liquiritigenin were examined using commercial assay kits.
Results: A short half-life (0.25-0.43 h) in serum was observed, while a longer estimation of half-life (26-77 h) was observed using urinary data. The flavonoid is predominantly excreted via non-renal routes (f_e values of 0.16-25%), and undergoes rapid and extensive phase II metabolism. Racemic liquiritigenin demonstrated a dose-dependent inhibition of α-amylase enzyme compared to its pure enantiomers which revealed more potent inhibitory activities. Racemic liquiritigenin showed moderate anti-proliferative activity on a HT-29 (human colorectal adenocarcinoma) cancer cell line that was dose-dependent and potent inhibitory effects on the cyclooxygenase-2 enzyme. The flavonoid did not inhibit the activity of cytochrome CYP 2D6 over the concentration range studied but was a potent anti-oxidant.
Conclusion: Stereoselective pharmacokinetics of liquiritgenin were demonstrated and the importance of examining stereospecificity in the pharmacological effects of liquiritigenin was determined.

48. Effect of Isoproterenol on Catabolism of Adenosine and Adenosine 5-'triphosphate in Systemic Blood *in vivo*

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Purpose: Previous studies have shown that metabolism of adenosine 5'-triphosphate (ATP) in red blood cell (RBC) may be a key factor

maintaining cardiovascular homeostasis. The study investigates the effect of cardiovascular injury on adenosine and ATP catabolism in systemic blood using a previously described freely moving rat model *in vivo*.

Method: The study was approved by the Dalhousie University Committee on Laboratory Animals (UCLA). After acclimatized to the experimental environment, Sprague Dawley (SD) rats were each given either isoproterenol (30 mg/kg) or saline (1 mL/kg) by subcutaneous (sc) injection. Blood samples were collected sequentially for up to 6 hours for measurement of red blood cell (RBC) concentrations of adenine nucleotides and plasma concentrations of adenosine and its oxypurine metabolites.

Results: We have found isoproterenol induced 50% mortality under the experimental condition. Plasma concentrations of adenosine (ADO) and uric acid (UA) and red blood cell (RBC) concentrations of adenosine 5'-diphosphate (ADP) and adenosine 5'-monophosphate (AMP) in RBC were significantly higher in the isoproterenol treated rats ($p < 0.05$ for all the comparison). On the other hand, plasma concentrations of hypoxanthine (HYP) were higher in the control group ($p < 0.05$), but there was no statistically significant changes in ATP concentrations in the RBC ($p > 0.05$).

Conclusion: Cardiovascular injury induced by isoproterenol resulted in breakdown of ATP to ADP and AMP in the RBC and also breakdown of ADO to UA in plasma and other tissues (supported in part by Dalhousie Faculty of Health Professions Research Development Grant and Pharmacy Endowment Foundation).

49. Lamotrigine Metabolism by UDP-Glucuronosyltransferases, UGT1A4 and UGT2B7, and their Role in Pediatric Toxicity Through Inadequate Glucuronidation

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Purpose: Lamotrigine (LTG) could be useful in childhood epilepsy. However, reports suggest that up to 80% of children with Dravet's Syndrome treated with LTG had seizures worsen, manifesting new seizure types not attributable to disease but characteristic of LTG overdose toxicity. The sole pathway of LTG metabolism and clearance is glucuronidation, specifically UDP-glucuronosyl transferases (UGT) 1A4 and 2B7. Since drug clearance by these isoforms does not mature for years after birth, we hypothesized that the mechanism of LTG toxicity in children is inadequate glucuronidation.

Method: Glucuronidation of LTG was measured using UHPLC-MS/MS in 91 livers (fetal 2, children 46, adults 41, elderly 5) with the specific inhibitors hecogenin and AZT used to determine UGT1A4 and UGT2B7 relative contribution to total LTG glucuronidation. Protein expression was measured by Western blot.

Results: The formation of LTG-2-glucuronide (LTG2G) was 0.433±0.025 nmol LTG2G/min/mg (mean±SEM) and activity was lower in children (0.34±0.04) compared with adults (0.49±0.03) but not significantly ($p=0.09$). Total activity was 0.330±0.02 and 0.080±0.006 in the presence of AZT and hecogenin, respectively, suggesting UGT1A4 accounts for 80% of metabolic clearance and UGT2B7 20%. Both UGT isoforms protein correlated with total activity ($r=0.40$ and 0.42 $p<0.0001$). The average UGT1A4 protein expression did not vary significantly but children had greatest range (14-fold) compared with adults (4.7-fold) and the elderly (1.3-fold). The UGT2B7 protein levels for children, adults and the elderly were 0.73±0.04, 0.75±0.04 and 1.11±0.09, respectively. The elderly had significantly higher UGT2B7 expression than children (Dunn's, $p<0.01$) and adults (Dunn's, $p<0.05$), with children having greatest variability (19-fold) as compared with adults (6.3-fold) and the elderly (1.6-fold). Protein levels of UGT1A4 and UGT2B7 were significantly correlated ($r=0.34$, $p<0.01$, Pearson).

Conclusion: These data confirm UGT1A4 and UGT2B7 are involved in LTG metabolism and that developmentally lower and more variable expression likely causes LTG toxicity in children.

AFPC POSTER PRESENTATIONS - JUNE 1, 2016

POSTER NUMBER	AUTHOR NAMES	ABSTRACT TITLE
AFPC - 1	***Waseem M. Abu-Ashour***, Laurie K. Twells, James E. Valcour, John-Michael Gamble	Diabetes and the Occurrence of Infection in Primary Care: A Matched Cohort Study
AFPC - 2	***Naif Aljuhani***, Lindsey Spryut, Randy Whittal, Arno Siraki	The Oxidation of the Anticancer Drug Metabolite, 6-Mercaptopurine Ameliorates Cu-Zn Superoxide Dismustase Activity: Potential Involvement of Peroxymonocarbonate
AFPC - 3	Renée Dagenais, ***Arden R. Barry***, Mary H. H. Ensom	The Bus Analogy: A New Analogy to Help Pharmacy Students Conceptualize the Well-Stirred Model
AFPC - 4	***Jam Bravo***, Mirando So, Karen J. Cameron, Cindy Natsheh, Gordon A. Tait	Descriptive Analysis of Fourth Year Pharmacy Students' Perspective on Virtual Interactive Case (VIC) Software
AFPC - 5	***Rene Breault***, Jill Hall, Sheila Walter, Ken Cor	Experiential Education in the PharmD for Practicing Pharmacists Program: Preceptor Experiences and Expectations
AFPC - 6	***Rene R. Breault***, Christine A. Hughes, Deborah Hicks, Theresa J. Schindel	Compensation Plan for Pharmacy Services: Communicating Change in Alberta
AFPC - 7	***Dion R. Brocks***, Ken Cor	The Relationship Between Grades in Prerequisite Pharmacy Courses and Pharmacy Grades at the University of Alberta
AFPC - 8	***Divna Calic***, Ryan G. Lillico, Ted M. Lakowski, Casey Sayre, Sheryl A. Zelenitsky	Significant Changes in Cefazolin Protein Binding During Cardiac Surgery with Cardiopulmonary Bypass
AFPC - 9	***Karen J. Cameron***, Salma Satchu, Jenny Chiu, Anna Chiu, Dhwani Raiyani, Eric Luloff, Andrea J. Cameron, Olavo Fernandes	Assessment of PharmD Student Performance on Standardized Medication Reconciliation Validation at Academic Hospitals
AFPC - 10	***Fong Chan***, Katherine Seto	Implementation of an Assessment Strategy Using Human Patient Simulation Technology to Evaluate Pharmacy Students
AFPC - 11	***Theresa L. Charrois***, Jay Mutch, Lydia Cheung, Jill J. Hall, Meagen M. Rosenthal, M. Ken Cor	Defining Characteristics of Successful Pharmacists: A Qualitative Study
AFPC - 12	***Gilles Leclerc***, Marie-Lou Deschamps, Antoine Lebrun, Michael Cardinal, Mathieu Nobert, Charles-Edouard Morel, Christiane Nathalie Geillon	eHealth Education: Anatomy of an Interprofessional Initiative
AFPC - 13	Justin Mak, ***Doret Cheng***, Cindy Natsheh	Entrustable Professional Activities (EPAs) for Pharmacy? A Literature Review
AFPC - 14	***Jenny Chiu***, Monica Lee	Comparison of Pharmacy Students' and Pharmacists' Activities using a Clinical Pharmacist Workload Measurement Tool
AFPC - 15	***Anna Cieślak***, Jocelyn Trottier, Melanie Verreault, Frederic Calon, Marie-Claude Vohl, Piotr Milkiewicz, Olivier Barbier	Docosahexaenoic Acid Activates Bile Acid Detoxification in Mice

AFPC - 16	***Chesarahmia Dojo Soeandy***, Faraz Salmasi, Jeffrey Henderson	Defining an Alternative Murine Model of Cerebral Ischemia: Focal Vasoconstriction via Endothelin-1
AFPC - 17	***Nyasha Gondora***, Michael A. Beazely, John G. Mielke	Chronic Early Life Social Isolation Affects Expression of TrkB and NMDA Receptor Proteins in a Sex-Specific Manner
AFPC - 18	***Kerry B. Goralski***, Steven R. Hall, Jay Toulany, David L. Jakeman	Jadomycins induce DNA Damage and Caspase-dependent Apoptosis in Human MDA-MB-231 Breast Cancer Cells
AFPC - 19	Arun K. Verma, Judith Soon, ***John Y. Groumoutis***	The Interprofessional Medication Reconciliation Program: A Quantitative Evaluation
AFPC - 20	***Arun K. Verma***, Judith A. Soon, Jackson Stewart	The Interprofessional Medication Reconciliation Program: A Qualitative Analysis
AFPC - 21	***Jill J. Hall***, Rene R. Breault, Sharon Marsh, Candace M. Necyk, Theresa J. Schindel	A Model of Innovative Integration in the Doctor of Pharmacy for Practicing Pharmacists Program
AFPC - 22	Michael B. Weale, ***Jennifer E. Isenor***, Melissa Helwig, Susan K. Bowles	Advancing and Evaluating the Drug Information Resources (DIR) Website
AFPC - 23	***Derek J. Jorgenson***, Eric J.L. Landry, Katherine J. Lysak	A Mixed Methods Evaluation of a Medication Assessment Clinic Located Within a Pharmacy School
AFPC - 24	***Deborah V. Kelly***, A. Nicole Pittman	Development of a Pharmacist-run Medication Therapy Services Clinic
AFPC - 25	Alexander D. Smith, Arnab Ray, ***Tara Klassen***	Classic Labs for a New Program: Development of Integrated Pathophysiology Activities for the Entry-to-Practice PharmD Curriculum
AFPC - 26	Alexander D. Smith, Arnab Ray, ***Tara L. Klassen***	Bandana Science: Peers in the Preparation for and Teaching of Pathophysiology in PharmD Entry to Practice Integrated Activities
AFPC - 27	***Mia G. Losier***, Megan E. Harrison, Emily K. Black, Heather L. Neville, B. Lynn Johnston, Kim A. Abbass, Kathryn L. Slayter, Ingrid S. Sketris	Point Prevalence Survey of Antimicrobial use at the Queen Elizabeth II Health Sciences Centre in Halifax, Nova Scotia
AFPC - 28	***Melissa Lu***, Brenna Shearer, Alberto Severini, Silvia Alessi-Severini	Survey of Knowledge and Attitude Regarding HPV Infection, Vaccine and Testing
AFPC - 29	***Katherine J. Lysak***, Shawna L. Berenbaum, Stephanie M. Mulhall, Jason P. Perepelkin, Yvonne M. Shevchuk, Jeff G. Taylor, Derek J. Jorgenson	Pharmacy Student Perceptions of a Medication Assessment Clinic Located Within a Pharmacy School
AFPC - 30	***Pedram Rafiei***, Azita Haddadi	Docetaxel Loaded PLGA Nanoparticles for Intravenous Application: Pharmacokinetics and Bio-distribution profile
AFPC - 31	Annie-Claude Couture, Sarah Girard, ***Marc-André Renaud***, Marie Vincent-Tremblay, Jean-Luc Dionne, Robert Bell, Michel Vallée, Robert Robitaille, France Varin, Philippe Bouchard	An Observational Study to Assess the Accuracy of Carboplatin Area under the Concentration-time Curve in Oncology Patients with Standardized Creatinine Measurement and Modern Formulas for Renal Function Estimation
AFPC - 32	***Miao Yan (Marilyn) Sun***, Tara Leah Klassen	Novel Missense Mutations in SCN1B as a Cause of Pediatric Epilepsy

Poster Session 2

CSPS and CC-CRS Posters

AFPC Posters

Thursday, June 2

Posters - Session 2

Thursday, June 2

Biomedical Sciences

50. Altered Cardiac Protein Expression of CYP2j in Mouse Models of Type I and Type II Diabetes

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Purpose: Arachidonic acid (AA) is metabolized by cytochromes P450 (CYP450) in different products such as epoxyeicosatrienoic acids (EETs) and 20-hydroxyeicosatetraeonic acid (20-HETE) known to have cardioprotective and cardiotoxic effects, respectively. Studies showed that Type I (T1D) and Type II (T2D) diabetes can alter the delicate balance between synthesis of EETs and 20-HETE by modulating protein expression of different cytochromes such as CYP4A, CYP4F and CYP2C. CYP4A and CYP4F metabolize AA in cardiotoxic 20-HETE and studies showed that expression is up-regulated in both types of diabetes. In contrast, CYP2C metabolizes AA in EETs, which are down-regulated in T1D and T2D.
Aim: To determine if T1D and T2D could also modulate the cardiac protein expression of CYP2j.
Method: Mouse models of T1D (streptozotocin) and T2D (C57BLKS/J-db/db) were used in this study. After sacrifice, ventricles were collected, washed in cold PBS and snap frozen. Total proteins were extracted using ice-cold lysis buffer. Western blots were performed to assess CYP2j protein expression.
Results: We obtained a significant decrease of murine protein expression of cardiac CYP2j in T1D group (0.5720 ±0.0328) and in T2D group (0.8029±0.0325) in comparison to control group (1.0460±0.0619).
Conclusion: This study showed that protein expression of CYP2j is decreased in both T1D and T2D. This modulation could disrupt the delicate balance between EETs and 20-HETE synthesis by pushing the balance towards the cardiotoxic side. This could contribute to the increased risk for cardiovascular disease associated with both types of diabetes.
Reference: Pilote S, Gélinas C, Patoine D, Drolet B, Simard C. Altered cardiac protein expression of CYP2J2 in mouse models of Type I and Type II diabetes. American Society for Clinical Pharmacology and Therapeutics 117th Annual Meeting. Clin Pharmacol Ther 2016;99 (Suppl 1):S47.
Acknowledgement: Carolanne Gélinas is the recipient of 2016 GSK/CSPS National Undergraduate Student Research Program Award.

51. Determining the Kinetic Parameters of SET7/9 Protein Lysine Methyltransferase

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Purpose: Histone lysine methylation is an epigenetic mechanism which can modulate gene expression and has been implicated in the various forms of cancer. The majority of enzymes responsible for catalyzing lysine methylation are within a family of enzymes containing a SET domain. The aim of this study is to determine the kinetic parameters of the lysine methyltransferase SET7/9 using liquid-chromatography and tandem mass spectrometry (LC-MS/MS) techniques.
Methods: Reactions are carried out *in vitro* using SET7/9 enzyme (New England Biolabs), S-adenosyl-L-methionine (Cayman Chemical), and a peptide based on the first 21 amino acids of the histone H3 protein (Epigentek). After 1 hour incubation at 37°C, reactions are heat killed at 75°C for 5 min. Samples are then taken and prepared for LC-MS/MS analysis. Analysis is performed using two separate assays, one to quantify histone modifications and one to quantify S-adenosyl-L-homocysteine (SAH), a co-product of the methylation reaction. The SAH production data are then used to calculate the kinetic parameters of the reaction, K_M and V_{Max} (SigmaPlot).

Results: The K_M for S-adenosyl methionine was determined from SAH data to be 0.48 +/- 0.07 pmol/min, the V_{max} for the reaction was 0.26 +/- 0.008 μM. The data from the histone modification assay gave a K_M of 0.22 +/- 0.03 μM and a V_{max} of 0.19 +/- 0.004 pmol/min.

Conclusion: The discrepancy between the values reported from each assay may indicate that SET7/9 can automethylate. Automethylation has been shown to alter or halt the activity of other methyltransferases, so this has implications for SET7/9. It is also of note that the histone modification assay showed that SET7/9 only catalyzed formation of monomethyllysine, making this the first time that this has been confirmed with such sensitive methods.

52. Hypouricemic Effects of Aqueous Extract of Erding Granules in Potassium Oxonate-Induced Hyperuricemic Mice

Jieyu Zuo[1], Hui Jian[2], Zhengyun Zuo[2], Shilin Yang[2] and Raimar Loebenberg[1].
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Erding Granules (GR) is a Traditional Chinese Medicine (TCM) preparation generally used for heat clearing and detoxifying listed in the Chinese Pharmacopeia (ChP). According to TCM of the formula might have anti-hyperuricemic properties.

Purpose: The study aimed to evaluate the effects of aqueous extract of Erding Granules (EG) on reducing serum levels of uric acid (SUA) in potassium oxonate-induced hyperuricemia mice. The extract's potency to inhibit uric acid production was assessed.

Method: An aqueous extract of EG following the ChP procedure was made. The extract was intragastrically administered to mice for 5 consecutive days. The hyperuricemia animal model was induced by potassium oxonate (PO) 1h before the last administration of the extract. Blood samples were taken 2h after PO injection and examined SUA and xanthine oxidase (XOD) activity in liver in 6 groups of male Kunming Mice (n=10 each), normal, untreated disease, positive control and three different doses (24g/kg, 12g/kg and 6g/kg) of the aqueous extracts were evaluated.

Results: Each group of aqueous extract of EG showed significantly reduced SUA but not in a dose dependent manner if compared to untreated disease mice ($P<0.05$). Only 24g/kg EG significantly influenced XOD activity in the liver ($P<0.05$).

Conclusion: The research demonstrates that aqueous extracts of EG had reducing effects on uric acid. EG might be used as a novel anti-hyperuricemia agent.

Acknowledgement: The authors acknowledge Scientific Grant of Jiangxi Province, China (No. 20144BDH80005 and 20151BBB70268) for financial support.

Group	Dose	UA (umol/L)	liver XOD (U/gprot)
Normal		152.80 ± 25.07 **	6.92±0.31
Untreated disease	450mg/kg	322.01 ± 35.08	7.57±1.13
Positive control	10mg/kg	190.45 ± 43.14 **	6.58±0.74
Erding	**24g／kg**	185.82 ± 43.37 **	6.17±0.84*
Erding	**12g／kg**	174.75 ± 43.16 **	7.02±0.73
Erding	**6g／kg**	264.58 ± 79.01*##	7.32±0.88

* compared with untreated group, * $P<0.05$, ** $P< 0.01$
# compared with Erding (12g/kg) group, # $P< 0.05$, ## $P< 0.01$

53. Compatibility Effects of Herb Composition in Reducing Uric Acid Level in Hyperuricemic Mice

Jieyu Zuo[1], Hui Jian[2], Zhengyun Zuo[2], Shilin Yang[2] and Raimar Loebenberg[1].
[1]Faculty of Pharmacy and Pharmaceutical Science, University of Alberta, Edmonton, Alberta, Canada; [2]Jiangxi University of Traditional Chinese Medicine

Introduction: Herb compatibility is one of the key characteristics of Traditional Chinese Medicine (TCM). Rather than monotherapy, TCM frequently uses multi-herb formulas to exert therapeutic action and modulate pharmacological effects.

Purpose: The study aimed to evaluate the anti-hyperuricemic effects between aqueous extracts of Erding Granules (EG) and aqueous extracts of the corresponding individual herbs.

Method: Erding formula is composed by whole plant extracts of Viola yedoensis Makino (Viola), Taraxacum mongolicum Hand.-Mazz.(Taraxacum), Lobelia chinensis Lour.(Lobelia) and root extract of Isatis indigotica Fort. (Isatidis). We extracted each plant extract following the EG preparation protocol

listed in the Chinese Pharmacopeia. The extracts were intragastrically administered to mice for 5 consecutive days. The hyperuricemia animal model was induced by potassium oxonate (PO) 1h before the last dose. Blood sample were collected 2h after PO injection and serum uric acid (SUA) was examined in 8 groups of male Kunming Mice (n=10 each), normal, untreated disease, positive control, Erding, Viola, Taraxacum, Isatidis and Lobelia.

Results: Each group of aqueous extract showed significantly reduced SUA (Erding, viola, taraxacum, Isatidis, and lobelia: 139.11±32.85, 156.78±25.56, 186.59±73.55, 217.89±49.51, and 234.48±26.16) as compared with untreated disease mice (285.94±26.67, P<0.01). The Erding extract worked better in reducing uric acid levels, especially compared with Isatidis and Lobelia (P<0.01).

Conclusion: Combinations of two or more herbs can be more effective in reducing uric acid level than using single herb extracts only.

Acknowledgement: The authors acknowledge Scientific Grant of Jiangxi Province, China (No. 20144BDH80005 and 20151BBB70268) for financial support.

Group	Dose (g raw material/kg)	UA（umol/L)
Normal		142.80±51.52＊＊
Untreated disease	450mg/kg	285.94±26.67
Positive control	10mg/kg	135.72±15.14＊＊
Erding	24	139.11±32.85＊＊
Viola	6	156.78±25.56＊＊
Taraxacum	6	186.59±73.55＊＊
Isatidis	6	217.89±49.51＊＊##
Lobelia	6	234.48±26.16＊＊##

*compare with untreated group, * P<0.05, ** P<0.01
#compare with Erding group, # P<0.05, ## P<0.01

54. The Cytotoxic Effect of Sphingosine-1-phosphate Towards Human Breast Cancer Cells *in vitro*

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Purpose: Sphingosine-1-phosphate (S1P), a bioactive sphingolipid metabolite, selectively induced apoptosis in breast cancer cells at concentration higher than 1 μM. At this concentration, both S1P receptors 1 and 2 (S1PR1 and S1PR2), which are the main S1P receptors in breast cancer, were expected to be blocked. S1P would accumulate inside the cells and induce apoptosis *via* its intracellular functions. However, little is known about the *in vivo* or *in vitro* degradation speed of S1P; and thus, we investigated whether using S1PR1 antibody could prevent cancer cell proliferation and survival through S1PR1 signaling due to reduced S1P concentration caused by degradation.

Method: We use CellTox™ Green Cytotoxicity Assay Kit to test the cytotoxicity effect of S1PR1 antibody alone over a wide range of concentration as well in combination with 0.1 μM, 1 μM and 10 μM S1P against breast cancer cell lines MCF7, SK-BR-3 and MDA-MB-231.

Results: No toxicity of S1PR1 antibody was observed against MCF7 and SK-BR-3 cells; however, it caused ~10% cytotoxicity towards the MDA-MB-231 cells at 18 ng/mL after 48 h of treatment. The combination of S1P and S1PR1 antibody exhibited ~24% cytotoxicity at 0.1 μM S1P and 32 ng/mL S1PR1 antibody towards the SK-BR-3 cells.

Conclusion: S1PR1 antibody alone could elude low cytotoxicity effect against human breast cancer depending on the cell type, antibody concentration and treat time. Meanwhile, its combination with S1P could cause higher cytotoxic effects against the breast cancer cells.

55. Structural Modeling of Voltage-gated Sodium Channels: Improving Molecular Diagnostics in Pediatric Epilepsies

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Purpose: There are >600 published epilepsy-causing variants in *SCN1A and SCN2A*, the genes encoding the voltage-gated sodium channels Nav1.1 and Nav1.2. Mutations in these gene cause severe epilepsy (Dravet/SMEI) as well as milder (GEFS+) and age limited (BFNS) syndromes. The majority are not inherited, arising *de novo* in the patient, and have not been previously reported. There is little correlation between disease severity and genotype, drastically limiting the interpretation of current gene tests for informed clinical decision making. We hypothesize that syndrome severity can be predicted

from the relative energetics (Gibb's Free Energy) of sodium channel destabilization during its transition from the closed to open state, resulting from the missense amino acid substitution.
Methods: Homology models of the human Nav1.1 and Nav1.2 were generated using Biovia Discovery Studio where bacterial voltage-gated sodium channel crystal structures in the open and closed conformations were used as templates. Personal epilepsy mutations were introduced via *in silico* mutagenesis and the energetic consequences were ranked to quantify the structural perturbation of each state.
Results: Stabilization and destabilization of both channel proteins was observed. This is highly mutation dependent, but independent of subunit or ultimately the position within the protein – homologous and adjacent positions having different energetic consequences. The bulk of mutations impact stability, with most destabilizing channel conformation.
Conclusion: Current bioinformatics tools have limited use in interpreting *SCN1A* and *SCN2A* mutations, such that new *in silico* tools to improve risk prediction accuracy are urgently required. Predictive structural modeling will allow refinement of molecular diagnostic interpretations, improving diagnosis, prognosis, and therapeutic decision making for truly personalized medicine.

56. Preferences for Donating Money to Support Drug Development Research Projects in a Sample of Canadian and U.S. Adults

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Purpose: Biomedical researchers are increasingly turning to project-based online fundraising (i.e. crowdfunding) as a complementary source of research funding. Researchers and organizations (e.g., universities, foundations, or biotech incubators) who seek to use this type of fundraising to finance both the pre-clinical and clinical stages of drug development research projects would benefit from being able to identify the types of projects that are most likely to appeal to donors.
Methods: To help inform the fundraising strategies adopted by researchers, we conducted an online survey of Canadian (n=413) and U.S. (n=401) adults. Using the self-explicated method (SEM) of preference elicitation, we estimated respondents' relative preferences for 43 different possible characteristics of fundraising campaigns aimed at supporting biomedical research. Respondents rated each characteristic based on its relative desirability and importance, and these ratings were used to calculate preference scores ranging from 0 (low preference) to 8 (high preference) for each characteristic.
Results: Average preference scores indicate that respondents had an overwhelming preference for donating to projects conducted by non-profit research organizations (mean=5.98, sd=2.96) instead of for-profit companies (mean=1.14, sd=2.21); projects that have the potential to yield a curative therapy (mean=6.08, sd=3.34); projects that focus on diseases with a high prevalence (*1 in 15*: mean=5.67, sd=3.17; *1 in 100,000*: mean=1.51, sd=2.89); and projects that focus on diseases with an early median age of onset (*Age 5*: mean=6.13, sd=2.92; *Age 70*: mean=0.82, sd=2.02)
Conclusions: Our results suggest that project-based online fundraising has significant potential to serve as a complementary source of research funding for many drug development projects, and could help to facilitate new business models for drug development. However, research projects focused on rare or age-related diseases and those conducted by biotechnology startups may have difficulty persuading donors to contribute financially.

57. FRET-labeled Self-assembled Nanoprobe for Rapid and Sensitive Detection of Postoperative Pancreatic Fistula

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Purpose: Postoperative pancreatic fistula (POPF) is the most serious and challenging complication following gastroenterological surgery. Activated pancreatic juice leaking from the organ remnant contains proteases that attack the surrounding tissue, potentially leading to severe inflammation, tissue necrosis, and fistula formation. However, it is difficult to observe pancreatic leakage during surgery and to evaluate the protease activity of

leaked fluid at the patient's bedside. Therefore, we have developed Heat Shock Protein (HSP) -based Förster resonance energy transfer (FRET) nanoprobe able to detect the activated pancreatic juice through the pancreatic proteases in drainage fluid.

Method: A variety of HSP-FRET nanoprobes were synthesized, and their reactivity with proteases was compared by fluorescence spectra. Drainage fluid was obtained from 6 patients who underwent gastrectomy or distal pancreatectomy. The FRET protein nanoprobes [10 μM] were added to the drainage fluid [80% v/v], and the mixture was monitored via real-time imaging using a digital camera relayed through a dichroic filter.

Results: The HSP-FRET probe was constructed by subunit exchange of each dye-labeled engineered HSP, resulting in a spherical nanocage of approximately 10 nm in diameter, which exhibited very high stability against degradation in blood plasma and no remarkable toxicity in mice. The efficiency of FRET was found to depend on both the dye orientation and the acceptor/donor ratio. Pancreatic proteases, including trypsin, α-chymotrypsin, and elastase, were quantitatively analyzed by fluorescence recovery with high specificity using the HSP-FRET nanoprobe. Furthermore, the HSP-FRET nanoprobe was sufficiently sensitive to detect POPF in the pancreatic juice of patients using only the naked eye within 10 min.

Conclusion: A novel nanoprobe has been developed for the detection of POPF based on the FRET mechanism that can be visually identified during gastroenterological surgery.

58. Using Photo-labelled Analogues of Ivacaftor to Probe for the Binding Site on Mutant CFTR

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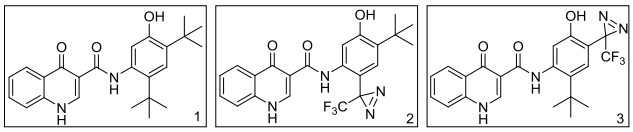
Purpose: The first approved Cystic Fibrosis (CF) therapeutic Ivacaftor (**1**) was discovered through a high-throughput functional screen measuring potentiation of the chloride channel CFTR. However, the nature of Ivacaftor's interaction with mutant CFTR is still under investigation. The aim of this study is to use photolabelling of Ivacaftor to probe for the binding site on mutant CFTR.

Method: A limited SAR study showed retention of the Ivacaftor potentiating activity with deletion of either of the *t*-Bu groups on **1**. This lead to a synthesis program to substitute the *t*-Bu groups for the photo-labelling diazirine motifs (**2**,**3**), to probe for Ivacaftor's binding site of on ΔF508 CFTR.

Results: Synthetic efforts have led to significant progress towards the synthesis of **3**

Conclusion: The potentiating activity of the photo-labelled analogues **2**, and **3** will be confirmed in functional assays before being tested in binding studies with F508-del CFTR containing liposomes.



59. Expenditures Guided by the Concept of Essential Medicines in Brazil: The Case of the Fibrates

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Purpose: The concept of essential medicines is internationally recognized as a health strategy to rationalize the use of medicines. Brazil has had an Essential Medicines Lists (EML) since 1964. In 2012, the number of items in the Brazilian EML (BN-EML) increased 54,4%. In that year ciprofibrate was included, although others fibrates were already covered. The aim of this study was to analyze the trends of Brazilian Federal Government expenditures with ciprofibrate and fenofibrate between 2008 and 2013.

Method: Data were extracted from the Brazilian Federal Government procurement database and the four last editions of the BN-EML. The analysis considered all medicines purchased by the federal government, from January 2008 to December 2013.

To measure expenditures, the total value of each purchase was calculated by multiplying the unit price by the volume and this value was adjusted for inflation using the Extended National Consumer Price Index (IPCA). Cost was presented in Reais (R$); 3 Reais = 1 Canadian dollars (CAD) (March 2016).

Results: The expenditures with both medicines increase over time. The Brazilian Federal Government expenditures with ciprofibrate from 2008 to 2014 amount 240 thousand Reais. In the same period, the expenditures with fenofibrate were 110 thousand Reais. The increase between 2011 and 2012 was higher for ciprofibrate than for fenofibrate. The government spent 27.392,11 Reais with ciprofibrate in 2011 and 75.879,27 Reais in 2012 (increase approximately of 177,0%). However, the expenditures with fenofibrate increase 12,2% from 2011 to 2012 (from 19.004,00 to 21.317,00).

Conclusions: The Brazilian Federal Government spent more with ciprofibrate than with fenofibrate, although the evidence of therapeutic benefits for the first one is lower and inconclusive. The inclusion of ciprofibrate on the NB-EML greatly increased the expenditures of the Federal Government with this class of medicine.

60. Discovery of 2-(1*H*-Indol-3-yl)-quinolines as Novel Inhibitors of Androgen Receptor Binding Function 3 (BF3)

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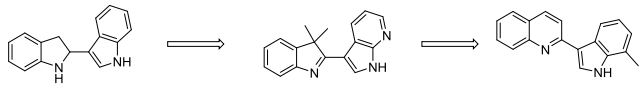
Purpose: Drug resistance is the major problem for the currently available antiandrogen prostate cancer drugs, Bicalutamide, Flutamide, Nilutamide and Enzalutamide which target the androgen binding pocket of AR. A functional surface pocket of the androgen receptor (AR) called binding function 3 (BF3) has been studied extensively as an alternative target to overcome resistance mechanisms. The goal of our research program is to design and synthesis of potent inhibitors of androgen receptor BF3.

Method: Previous work using *in silico*-guided screening led to the discovery of 2-(indol-3-yl)-indoline **1** as potent BF3 inhibitor which showed excellent antiandrogen potency and anti-PSA activity as well as significant reduction of tumor growth in prostate cancer xenografts. However, this series of compounds were found to be chemically unstable owing to their ability to undergo racemization under acidic conditions and the tendency to readily oxidize. Our synthetic efforts led to the identification of a more stable, second series of BF3 inhibitors **2** featuring two heteroaryl moieties connected in a flat spatial arrangement as the key structural requirement.

Results: We applied this key structural feature to generate the third series of BF3 inhibitors, the indolyl-quinoline series **3**. In which, compound VPC13566 was found to be effective in inhibiting AR-transcriptional activity *in vitro* in prostate cancer cell lines including an enzalutamide-resistant cell line. It also showed significant inhibition of tumor growth in prostate cancer xenografts. Results from the structure activity and relationship of the indolyl-quinoline series and lead optimization process will be presented.

Conclusion: Our results reinforce that targeting alternative sites other than the androgen binding site on the AR may help to circumvent the drug resistance problem in prostate cancer treatment. The lead compounds identified from the indolyl-quinoline series has clinical potential for the treatment of drug-resistant forms of prostate cancer.



61. Novel Antimicrobials Derived from Parasitic Nematodes

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Biochemistry; [3]Freie Universität Berlin, Institute for Microbiology and Epizoonotics; [4]Humboldt-Universität zu Berlin, Institute for Biology, Berlin, Germany

Purpose: Increasing antibiotic resistance in pathogens resulting in less effective antibiotics poses a severe threat to human health, highlighting the urgency for the development of novel antimicrobial agents. Antimicrobial peptides (AMPs) are an ancient component of innate immunity, distributed across all multicellular organisms, providing protection against various pathogens. Parasitic nematodes are widespread in nature, infecting humans and animals alike. As nematodes induce chronic infections that comprise tissue migrating life stages without inciting overt inflammatory responses, we hypothesize that intestinal nematodes release factors that interfere with the host mircobiota and thus exhibit antimicrobial activities. The aim of our studies is to test excreted and secreted products (ESPs) from parasitic nematodes for antimicrobial activity.
Methods: ESPs are collected from *ex vivo* cultured nematodes (*A. suum, T. suis, H. polygyrus*), fractionated by adsorption chromatography and methanol gradient elution, separated by gel electrophoresis, and tested for antimicrobial activity. Those fractions demonstrating antimicrobial activity are then subjected to peptide sequencing by liquid chromatography-tandem mass spectrometry analysis.
Results: Gel electrophoresis reveals numerous proteins and peptides recovered from ESPs. Radial diffusion assay with ES fractions demonstrate broad antimicrobial activity against gram$^+$ and gram$^-$ bacteria. Peptide sequencing reveals the presence of *Ascaris suum* anti-bacterial factor epsilon (ASABF-ε) in *A. suum* larval ESP, previously described only at the transcriptional level in adult *A. suum* in culture.
Conclusion: Preliminary results indicate nematode ESPs possess potent antimicrobial activity. Furthermore, this is the first report of ASABF-ε present in *A. suum* ESPs, suggesting its contribution to observed antimicrobial activity. Ongoing efforts are aimed at characterizing specific factors responsible for observed antimicrobial activities and whether these factors interfere with invasion and replication of pathogenic bacteria. Future studies will explore the mechanisms of interference and therapeutic potential of nematode-derived antimicrobials in infectious disease models.

Clinical Sciences & Pharmacy Practice

62. Co-prescription of Antipsychotic and Antiparkinson Medications: Adherence to Guidelines and the STOPP (Screening Tool of Older Persons' Potentially Inappropriate Prescriptions) Criteria in Beneficiaries of the Nova Scotia Seniors' Pharmacare Program

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Purpose: To study the trends in co-prescription of antipsychotic and antiparkinson medications for older persons and determine adherence to guidelines and STOPP criteria. We had two hypotheses 1) the number of potentially inappropriate prescriptions were frequent 2) the likelihood of potentially inappropriate prescribing was associated with patient characteristics (age, sex) and year of prescription.
Methods: We conducted a retrospective observational study and determined the dispensing of antipsychotic and antiparkinson medications for beneficiaries of the NS Seniors' Pharmacare Program aged ≥ 66 years from April 1, 2009 to March 31, 2014. The STOPP criteria (D6) recommends quetiapine and clozapine in those with parkinsonism or Lewy Body Disease and considers other antipsychotics potentially inappropriate. The US National Parkinson's Foundation categorized antipsychotics as first line (quetiapine and clozapine), second line (other atypical antipsychotics) or third line (typical antipsychotics). We determined the number of beneficiaries co-prescribed ≥ 30 days supply of both antipsychotic and antiparkinson medications, type and dose of medications and predictors of potentially inappropriate prescribing.
Results: 3838 beneficiaries were dispensed an antiparkinson medication, with 554 (14.4%) also using an antipsychotic. Approximately 40% of prescribed antipsychotics were first line (quetiapine and clozapine). 27.7% were second line (aripiprazole, olanzapine and risperidone) and 32.3% of the antipsychotics prescribed were potentially inappropriate. The global Wald chi-square test showed that an association between first choice

therapy and age group was statistically significant (p=0.0182). Patients 80-84 years had an odds ratio of 2.2 (95% CI 1.1 -4.4) vs. 66-69 years. The odds ratio of first choice therapy was 1.835 (95% CI 1.31-2.58) for men compared to women.

Conclusions: 62.7% of patients receiving antipsychotics received first or second line therapy with 32.3% receiving therapy deemed potentially inappropriate. Further work is needed to determine the reasons for the gap between guidelines and prescribing, and to determine strategies for improvement.

Disclaimer: "This study is based in part on de-identified data provided by the provincial ministries/departments of health. The interpretation and conclusions contained herein do not necessarily represent those of the provincial governments or ministries/departments of health. We acknowledge Health Data Nova Scotia for making the data available"

Acknowledgement: Sara Rehan is the recipient of 2016 GSK/CSPS National Undergraduate Student Research Program Award.

63. An Evaluation of the Quality of iPhone Applications for Hypertension Self-Management

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Purpose: Patient-oriented HTN applications vary significantly in functionality, from tracking blood pressure(BP) to education. It is critical to identify higher quality HTN self-management applications that could help patients. The primary objective was to review the quality of HTN self-management apps that included BP logs.

Methods: The Canadian Apple App Store was searched May 22 - July 28, 2015 using the keywords hypertension and blood pressure. HTN apps were given an aggregate quality score(max score:46) after appraisal of functional characteristics, BP tracking features, data validation, analytical features, and content trustworthiness. Apps with an educational component were given an educational quality score(max score: 29).

Results: Of 902 apps screened, 71 were analysed (n: 36 paid, average cost CAD$1.95[SD: $1.16]). The mean aggregate quality score was 16.8(SD: 6.8). Thirteen apps contained an educational component, with quality scores ranging from 1-14 out of 29. Free compared to paid apps scored significantly higher in analytical features, quality assurance, and aggregate quality score. Seventeen apps had a privacy policy, and 38 apps were updated in the past year. Few apps allowed BP goal-setting(n=9), reminders(n=19), tracked exercise(n=9) or diet(n=6). When BP readings were in alert ranges, only 4 apps suggested an appropriate course of action. There was a positive correlation between apps that had medication or weight tracking; BP categories; statistical analysis, with a higher aggregate quality score($P<0.001$).

Conclusions: HTN self-management applications range in quality and functionality. The average app was of poor quality and few contained an educational component. Even apps with an educational component often had unreliable quality. Thus, there is opportunity for leaders in hypertension management to develop a high quality, evidence-based application targeted to Canadians.

Acknowledgement: GSK/CSPS National Undergraduate Student Research Program Award Recipient, presented at the University of Alberta Faculty of Pharmacy and Pharmaceutical Sciences 2015 Research Day held on November 27, 2015.

64. How is Uncertainty in Risks and Benefits Presented in Patient Decision Support Interventions?

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Purpose: Overtreatment, including treatment misaligned with patient preferences, is a source of waste contributing to healthcare unsustainability. Patient decision support interventions (PDSIs) aim to improve patients' knowledge and yield choices more aligned with patients' preferences. The International Patient Decision Aid Standards (IPDAS) group recommend that uncertainty in evidence be described, but provide limited guidance on how. There are two levels of uncertainty: 1st order, which is the randomness of future events (i.e. the risk), and 2nd order, the imprecision in risk estimates. We sought to understand how uncertainty is described in PDSIs and highlight heterogeneity in approaches to presenting uncertainty due to a lack of

clear recommendations.
Methods: We reviewed all uncertainty statements around risks and benefits within all PDSIs available in three registries (Ottawa Hospital Research Institute, Choosing Wisely, Option Grid Collaborative). We developed a framework to classify these statements by their presentation of uncertainty, and their alignment with IPDAS guidance.
Results: 425 PDSIs were included. The PDSIs reviewed ranged in the number of options they presented to people from 2 to 16, and in the number of harms (0 to 31) and benefits (0 to 16) they included. The number of harms described outweighed the benefits. The predominant method of presenting first order and second order uncertainty was qualitative. When first and second order uncertainty was combined, there were multiple ways of describing uncertainty. This study examines the percentage of statements of uncertainty that met IPDAS guidelines and addresses the considerable variation in conformity.
Conclusion: There is considerable heterogeneity in the methods used to convey uncertainty around risks and benefits to patients. This heterogeneity is a product of a lack of evidence about how best to communicate uncertainty. There is an urgent need for more research into the evaluation of methods for communicating uncertainty to patients and its impact on patient preferences.
Acknowledgement: Madelaine Bell is the recipient of 2016 GSK/CSPS National Undergraduate Student Research Program Award.

65. Alcohol Misuse and Medical Cannabinoids Use: Interactions Clinical Toxicology Aspects

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Purpose: Cannabinoids are derived from the *Canabis sativa* which contains more than 60 cannabinoids. The primary psychoactive cannabinoid is delta-9-tetrahydrocannabinol (THC, dronabinol). THC interacts with cannabinoid-like ligands as well as multiple receptors in both the periphery and central nervous system. A spray containing THC and cannabidiol, nabiximols, is approved in Canada as adjunctive analgesic treatment in adult patients with advanced cancer who experience moderate to severe pain.
Objectives: To describe the effects of cannabis use in 30 patients suffering from Crohn's Disease (CD). The study was performed in an Israeli clinic and the blood samples analysis has been performed in my lab.
Methods: In this retrospective observational study we examined disease activity, use of medication, need for surgery, and hospitalization before and after cannabis use in patients with CD. Disease activity was assessed by the Harvey Bradshaw index for Crohn’s disease.
Results: The average Harvey Bradshaw index improved from significantly in 2/3 of patients.
Conclusions: The results indicate that cannabis may have a positive effect on disease activity, as reflected by reduction in disease activity index and in the need for other drugs and surgery. Prospective placebo-controlled studies are warranted to fully evaluate the efficacy and side effects. In addition, the misuse of alcohol in patients taking medical cannabinoids can be deadly.
Given the legal status of marijuana, differences in cannabinoid concentrations across strains of cannabis, the lack of information about potential drug-drug interactions, alcohol misuse and cannabinoids' interaction, it is the role of pharmacologists-toxicologists to work with physicians to monitor the use of cannabinoids.
1 - evaluate the interaction of alcohol in medical cannabinoids;
2 - negotiate ethical problems in using medical cannabinoids and their therapeutic monitoring;
3 - identify hepatocytotoxicity as a result between misuse of alcohol when using other therapeutics and medical cannabinoids.

Drug Delivery & Pharmaceutical Technology

66. Development of Antibody-modified Chitosan Nanoparticles for the Targeted Delivery of siRNA Across the Blood-brain Barrier as a Strategy for Inhibiting HIV Replication in Astrocytes

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Purpose: HIV infects brain astrocytes using them as a reservoir. There are currently no approved nanomedicines for the treatment of HIV/AIDS in the brain mainly due to the presence of the blood-brain barrier (BBB). Utilizing receptor-mediated transport systems, nanocarriers can deliver adequate therapeutic doses to the brain. SART3 is a cellular gene that encodes Tip110, a protein which regulates HIV-1 Tat transactivation. Moreover, hCycT1 encodes cyclin T1, which also interacts with Tat to activate the elongation of RNA polymerase II. The goal of this study was to develop dual antibody (Ab) modified chitosan (CS) nanoparticles (NPs) for the targeted delivery of SART3 and hCycT1 siRNA across the BBB.
Method: CS-NPs are an ideal delivery vehicles because they are biodegradable and have the ability to open tight junctions. siRNA-loaded CS-NPs were formulated via ionotropic gelation with tripolyphosphate (TPP). NPs were then decorated with transferrin (OX26-TfR) and bradykinin b2 (BDKRB2) receptor antibodies. The formulation was optimized to the mass ratio of 750:150:25:5 (CS:TPP:siRNA:Ab). The physicochemical properties such as surface morphology, mean particle diameter, zeta potential, and encapsulation efficiency were investigated. Most importantly, the targeting effect of siRNA-Ab-NP was evaluated in U138-MG cells. siRNA knockdown efficiency was determined at mRNA levels.
Results: Our CS-NPs have an average size of 249.6 ± 5.4 nm and a zeta potential of -40.04 ± 0.16 mV. CS-NPs showed a great siRNA stability and entrapment efficiency as determined by electrophoresis and PicoGreen assay, respectively. TEM images confirmed NPs spherical shape. Cell uptake studies showed almost double the uptake of our siRNA-Ab-NP in comparison to the control. Cell viability studies using MTS showed low cytotoxicity. Finally, RT-PCR data showed a significant gene knockdown efficiency by 64.5 ± 5.7% for SART-3 and 47.3 ± 8.9% for hCycT1.
Conclusion: Our platform demonstrates potential utility for the treatment of HIV infection in the central nervous system.
Acknowledgment: Karam Al-Bayati is grateful for the GSK/CSPS National Undergraduate Student Research Program Award.

67. Preclinical Efficacy Study of a Podophyllotoxin-carboxymethylcellulose Nanoparticles Against Orthotopic and Metastatic Tumors

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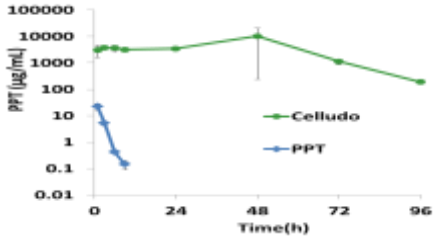
Purpose: Podophyllotoxin (PPT) is a highly efficacious drug against multi-drug resistant (MDR) tumors. However, due to its high toxicities and poor solubility, it cannot be used clinically. We developed a nanoparticle (NP) drug delivery system to enhance activity of PPT against MDR tumors by modulating the cellular uptake pathway.
Methods: Nanoparticle dosage form of PPT (Celludo) is developed by covalently conjugating PPT and polyethylene glycol (PEG) with acetylated carboxymethyl cellulose (CMC-Ac) via ester linkages. The optimal composition of the conjugate with a PPT/PEG ratio of 2 mol/mol self-assembled into 20 nm particles in saline. The formulation was tested for its efficacy and safety against MDR tumor models in mice. The pharmacokinetics (PK) is studied properly by measuring the concentrations of released and conjugated PPT in blood.
Results: The PK study also showed that the celludo blood circulation time was significantly extended compared to the free drug, with a 22.9 times higher half life, 3110 times higher area under the volume of distribution, 15.9 times higher maximum concentration and 26.3 times higher mean residence time, and substantially lower value of the clearance. Celludo also was found to be highly efficacious against 4T1 orthotopic breast cancer in mice. Celludo treatment resulted in a 97% growth

inhibition of the primary tumor and complete elimination of lung metastases compared to 40% and 55% tumor growth inhibition and 8.5% and 6.8% lung metastasis with native PPT and CBZ treatment respectively. In another model, lung metastasis was induced by i.v. injection of EMT6-AR1 cells. Significant Celludo localization was found in the metastatic nodules in the lungs compared to normal lung and other tissues.



Conclusion: The 20 nm particles (Celludo) showed enhanced PK and exhibited 5- to 20-fold increased tumor delivery and significantly improved efficacy against subcutaneous models of MDR tumors in mice compared to, native PPT and the standard taxane chemotherapies, with minimal toxicity.

68. Production of Size-Tunable PLGA Nanoparticle Drug Delivery Systems using Microfluidic Technology

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Purpose: Conventional methods for producing PLGA nanoparticles pose numerous challenges such as maintaining stable diameters below 100 nm, reproducibility, and scale-up. The NanoAssemblr™ platform provides an automated microfluidics-based technology capable of reproducible, and scalable manufacture of nanoparticles. Here, we describe the production of PLGA nanoparticles using the NanoAssemblr™ microfluidic platform. We further describe strategies to tune the size of the nanoparticles and investigate the encapsulation of a hydrophobic model drug Coumarin-6.
Method: PLGA nanoparticles were manufactured by microfluidic mixing using the NanoAssemblr™ bench-top instrument (Precision NanoSystems, Inc., Vancouver, Canada). PLGA of varying molecular weights were dissolved in acetonitrile at desired concentrations. Similarly, aqueous solutions containing suitable stabilizer were prepared at desired concentrations. PLGA nanoparticles were formed by controlled nanoprecipitation achieved by precise control over the microfluidic mixing of two-inlet fluid streams containing PLGA in acetonitrile and aqueous solutions of stabilizer, through proprietary staggered herringbone mixing (SHM) apparatus. Coumarin-6 was loaded into PLGA nanoparticles at desired drug:polymer (w/w) ratios.
Results: Microfluidic mixing enabled the rapid and consistent manufacturing of PLGA nanoparticles having stable diameters as low as 70 nm. Single variables, such as aqueous:organic flow rate ratio (FRR), total flow rate (TFR), and PLGA concentration were found to have a significant impact on the size of the resulting nanoparticles. For example, an increase in the PLGA concentration led to an increase in nanoparticle size whereas increasing the TFR led to a decrease in nanoparticle size. Coumarin-6 was successfully loaded into PLGA nanoparticles with an encapsulation efficiency above 70%.
Conclusions: Herein, we have successfully demonstrated the potential of microfluidics technology in the manufacture of PLGA nanoparticles for delivery of small molecule therapeutics.

69. Microfluidics-Based Seamless Manufacture of RNA-Lipid Nanoparticles from Discovery to Clinic

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Purpose: Recently, lipid nanoparticles (LNPs) have gained interest in gene therapy as safe and efficient vectors for delivery of nucleic acids. However, the translation of these nanoparticles from the screening phase to clinical nanomedicine candidates has been limited due to challenges in optimization during scale-up. Here, we describe the ease in manufacturing siRNA-LNPs using the microfluidics-based platform from discovery through pre-clinical development.
Methods: siRNA was encapsulated into LNPs using the NanoAssemblr™ Benchtop instrument (Precision NanoSystems, Inc., Vancouver, Canada) at desired aqueous:organic flow rate ratio and total

flow rate. Using the same parameters, siRNA was encapsulated into LNPs using a small volume discovery instrument and a large volume pre-clinical development instrument. The siRNA-LNPs were characterized for their size, PDI, and encapsulation efficiencies across the three NanoAssemblr™ instruments. In further studies, knockdown of target genes using siRNA-LNPs was investigated in primary mixed cortical neuronal cultures.

Results: siRNA was successfully encapsulated into LNPs across the NanoAssemblr™ platform. LNPs prepared using the NanoAssemblr™ Benchtop instrument exhibited small size (~ 50 nm), and low PDI (< 0.1) which was similar to siRNA-LNPs prepared using the low volume discovery instrument and the pre-clinical development instrument. Encapsulation efficiency of siRNA in LNPs was similar (> 95%) across all three NanoAssemblr™ instruments. This provides for the seamless scale-up of optimized conditions from the discovery phase (100 - 1000 μL), to the benchtop instrument (1 mL - 15 mL), up to the pre-clinical stage (10 mL - 1000 mL). In further studies, siRNA-LNPs manufactured using the NanoAssemblr™ platform showed effective knockdown (> 75%) of the target gene PTEN in primary mixed cortical neuronal cultures at low siRNA concentrations of 100 ng/mL.

Conclusions: The results exhibit the potential of the NanoAssemblr™ microfluidics-based platform to aid in the seamless scale-up of RNA-LNPs from discovery to clinic.

70. Microfluidics-Based Platform for the Scale-up of Lipid Nanoparticles for Delivery of Nucleic Acid Therapeutics

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Purpose: Recently, lipid nanoparticles (LNPs) have gained interest as efficient carriers for delivery of nucleic acids. However, their transition from bench to clinic has been slow due to numerous challenges such as poor reproducibility and scalability. Here, we bridge that gap by describing the robust manufacture of LNPs using the microfluidics-based NanoAssemblr™ platform, and the ease in scaling production to clinical-scale through microfluidic mixer parallelization.

Method: siRNA was encapsulated into LNPs using a single microfluidic mixer on the NanoAssemblr™ Benchtop instrument (Precision NanoSystems, Inc., Vancouver, Canada) at varying aqueous:organic flow rate ratios and total flow rates to reach an optimized formulation. The optimized formulation was transferred to a scale-up system comprising a continuous flow pumping system with 8 single-mixer microfluidic chips arrayed in parallel using a manifold. This scale-up system utilizes parallelized microfluidic mixers to maintain identical reaction conditions and increase production throughput. The initial version of the NanoAssemblr™ Scale-up GMP system is designed to manufacture 5.75L per hour and incorporates a disposable fluid path eliminating the need for costly and time consuming cleaning validation.

Results: siRNA-LNPs prepared using a single mixer at total flow rate through the microfluidic chip of 12 mL/min showed similar size and PDI compared to siRNA-LNP made using 2x microfluidic chips and 4x microfluidic chips arrayed in parallel. Size and PDI of siRNA-LNPs produced using the single mixer NanoAssemblr™ Benchtop instrument was similar to that produced using the 8x scale-up system further validating the use of microfluidic parallelization as a mechanism for rapid and seamless scale-up.

Conclusion: This study reflects the potential of microfluidics-based technology in bridging the gap from discovery to clinic for nanoparticle-based delivery vectors.

71. Lanthanide Compounds for the Treatment of Bone Density Disorders

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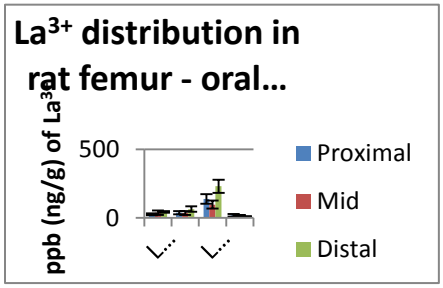
Purpose: Bone is constantly being remodelled through the process of bone formation and bone resorption by osteoblasts and osteoclasts, respectively. An imbalance in this remodelling process preferentially favouring bone resorption results in decreased bone mineral density, seen in bone density disorders such as osteoporosis.

Lanthanum (La) is a pharmacotherapeutic agent of interest because it preferentially accumulates in bone tissue, stimulates osteoblast proliferation and inhibits osteoclast activity. This is anticipated to be a more effective multi-pronged approach than currently available therapies like bisphosphonates. Preliminary *in vitro* and *in vivo* data has shown that our novel La compounds exhibit good bioavailability, biocompatibility, and are incorporated into the bone matrix, unlike bisphosphonates which are only surface-bound to bone.

Methods: We have performed an acute 1-month oral dosing study of 2 La compounds, La(XT) (in aqueous solution) and $La(dpp)_3$ (as CMC suspension or lipid formulation) to assess the bone-uptake of lanthanum, the effect on bone mineralization and architecture, and the biodistribution and toxicity of the compounds. The biodistribution of La within plasma, organs, and the femur was determined via ICP-MS, while initial spatial mapping of lanthanum within bone was performed by K-Edge subtraction imaging using the BMIT 05B1-1 beamline at the Canadian Light Source (Saskatoon).

Results: *In vivo* evaluation indicates that both lanthanum compounds are well-tolerated at 50mg/kg, lanthanum is rapidly cleared from the plasma, and, most importantly, targets bone tissue and exhibits a depot type of accumulation.



Conclusion: Two lanthanum-based lead compounds were examined as a potential therapeutic agent in the treatment of bone density disorders. It was shown that La accumulates in the bone after dosing, with LaXT showing slightly higher uptake. The current study suggests that chronic *in vivo* experiments need to be performed to assess their drug candidacies, with the long-term goal of transfering these treatments for human use.

Acknowledgement: Meghanne Rieder is a winner of the GSK/CSPS National Undergraduate marcStudent Research Award

72. Topical Nifedipine for the Treatment of Raynaud's Syndrome

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Purpose: Raynaud's syndrome causes arteriolar vasospasm upon cold exposure, with fingers and toes most commonly affected. Nifedipine, a vasodilator and calcium channel blocker is the drug of choice in treating Raynaud's syndrome. Daily oral administration of nifedipine to reduce the number and severity of attacks can cause adverse effects such as headache and dizziness, therefore a topical formulation is a desirable alternative. Nifedipine is poorly water soluble and subject to rapid photodegradation. A topical o/w emulsion was formulated. In order to further improve the photostability, rutin, quercetin or butyl methoxydibenzoylmethane (BMDBM) alone or in combination were incorporated.

Methods: Nifedipine emulsions were exposed as thin films to UVA light (450 W/cm^2). Drug analysis was performed by RP-HPLC. Mass spectrometry was done using a Triple Quadrupole/Linear Ion trap mass spectrometer with an electrospray ionization source. Physical stability was determined by accelerated sedimentation using a photocentrifuge (LumiSizer) at 42°C over 12h. Permeation studies were performed at 32°C in static vertical diffusion cells holding StratM model skin membranes.

Results: Rutin at 0.5% (w/w) did not improve the stability of nifedipine to UVA light, however quercetin at 0.5% (w/w) and BMDBM at 3% (w/w) alone or in combination maintained nifedipine concentration (>70%) after 4h UVA exposur.e Mass spectrometry analysis indicated dehydronifedipine and dehydronitrosonifedipine are the primary nifedipine photodegradation products formed, regardless of photostabilizer incorporated. Sedimentation analysis by photocentrifuge showed slight differences in tendency to phase separation at 42°C over 12hr between the emulsions containing the various photostabilizer additives. Assessment of nifedipine diffusion across artificial skin membranes indicated that all of the formulations enabled nifedipine diffusion, with the nifedipine-quercetin cream showing greatest cumulative diffusion over 4hr.

Conclusions: We have prepared stable topical

nifedipine emulsions with demonstrated photostability that promote nifedipine uptake across model skin.

73. Evaluation of Carbopol 934P NF Microemulsion-Based Gel Formulations for Topical Drug Delivery of Diclofenac Sodium

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Purpose: The aim of the current research work was to improve the transdermal delivery of diclofenac sodium, a poorly water-soluble drug. Different formulations were prepared and vitro evaluated.
Methods: A micro emulsion (ME) was prepared using Labrasol, Transcutol P and Lauroglycol FCC. For enhancing the viscosity, Carbopol 934P NF was used to form an ME-based gel. The prepared formulations were characterized for physical appearance, droplet size, Zeta potential, Freeze-thaw cycle, phase separation, pH, conductivity, drug content, staining solubility test, transmission electron microscopy and in-vitro drug release using Franz diffusion cells. One-way ANOVA and Tukey's test were used to establish statistical significance at $p>0.05$. A comparison between a commercial formulation and a Carbopol gel containing free drug only are presented.
Results: Mean droplets size for ME and ME-based gel-systems were 114.4± 0.472 nm, and 178± 2.46 nm respectively, whereas the zeta potential values were -33.3 ± 0.64 mV for the former and -33 ± 0.40 mV for the latter. No significant variation in the pH and no physical appearance alterations has been observed after subjecting the formulations for stability tests. Further, TEM images for drug-loaded ME and its gel exhibited nano-droplets that were almost spherical in shape. The release rate of diclofenac sodium formulated as ME or as ME gel had the highest release values (76.67 ± 8.63% and 69.28 ± 7.14 % after 6 hr) respectively. This was statistically significant ($p< 0.0001$) compared to the control and the marketed formulation.
Conclusion: The result suggested that both ME systems are potential vehicles for penetration enhancement of diclofenac sodium as a topical delivery system. However, the ME-based gel seems to be preferable due to its pH profile and higher viscosity to be handled as topical dosage form.

74. Isolation of Primary Murine Brain Endothelial Cells, Pericytes and Astrocytes

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Purpose: *In vitro* models of the blood-brain barrier (BBB) are essential tools for screening drugs targeted to the central nervous system. Although several useful cell-based BBB models have been developed, factors related to their complexity, cost and time limit their application for drug transport studies. Therefore, we sought to develop a simple, versatile, reproducible and biorelevant tri-cellular-based BBB model, using murine primary brain endothelial cell (EC), pericyte and astrocyte cultures.
Methods: ECs were isolated from brain capillaries of 8-12 week old wild-type C57BL/6 mice, whereas pericytes and astrocytes were prepared from the brains of 1-5 day old mice. We used a simple 3-step protocol that consisted of mincing/homogenizing the brain. Next, the homogenate was digested and brain microvessels were separated by Percoll gradient centrifugation. Brain capillaries were seeded onto appropriate supports. Three different media, specific to the culture of each cell type, were used. The purity of EC, astrocyte and pericyte cultures was assessed by flow cytometry and immunocytochemistry. The trans-endothelial electrical resistance (TEER) of EC cultures was evaluated with the ECIS System (Applied BioPhysics).
Results: Highly enriched EC cultures were obtained 7 days post-plating following addition of puromycine to the culture medium. These cells expressed the endothelial markers MCAM and PECAM. They displayed high TEER values (4000 Ω), suggesting establishment of tight junctions. EC cultures responded to inflammatory stimuli (TNF) by upregulating their expression of the cell adhesion molecule ICAM-1. Pericytes and astrocytes were successfully obtained and enriched from the brains of newborn mice. They were cultured for 3-5 weeks, at which time they expressed specific markers MCAM and PDGFR-β for pericytes and GFAP and GLAST-1 for astrocytes.
Conclusion: We successfully isolated three major

constituents of the mouse BBB using a single protocol. All cultured cells retained their biological features and will now be used to develop a BBB model.

75. Hydroxychloroquine Attenuated Vaginal Tissue Inflammation and T-cell Activation in vivo

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Purpose It has been revealed that women with natural resistance to HIV infection demonstrating an immune quiescence (IQ) phenotype of female genital tract, presenting reduced HIV target cells, low levels of HLA-DR positive activated T cells and reduced levels of pro-inflammatory cytokines. We developed a novel biocompatible vaginal implant for the delivery of the immunomodulatory drug hydroxychloroquine (HCQ) to induce IQ to evaluate its effectiveness in suppressing Nonoxynol-9 (N9) induced inflammation and T-cell activation in a rabbit vaginal mucosal model.
Methods Reservoir-based polyurethane implants were fabricated via hot-melt injection molding, embedded with a radio-frequency identification micro-transponder for real-time tracking. The device containing HCQ (60 mg) was non-invasively implanted in the vaginal tract of New Zealand White rabbits for 6 days and challenged with 1 mL 4% N9 gel for 24 hours. HCQ levels and inflammatory cytokine production in cervicovaginal lavage (CVL) was quantitated using HPLC and sandwich ELISA. Levels of RLA-DR (rabbit equivalent of human HLA-DR) from isolated vaginal mucosal T-cells was investigated by flow cytometry.
Results X-ray analysis showed the implant remaining within the rabbit vaginal tract for over 40 days. HCQ exhibited an average release rate of 10.67 µg/mL per day for 7 days. The expression of RLA-DR on isolated vaginal CD4+ and CD8+ T cells in N9-challenged HCQ pre-treated rabbits were restored to basal levels similar to the naïve group. Lower amounts of immune cell recruitment were observed in HCQ pre-treated rabbits with significantly attenuated levels of IL-1β and IL-8 in CVL.
Conclusion We designed a novel non-invasive implantable device for delivering HCQ in rabbits intravaginally capable of suppressing N9-induced inflammation and T-cell activation. This non-cytotoxic system may be suitable for the evaluation of other drug candidates for sexually transmitted infections.

76. pH-Sensitive Nanomicrobicide for the Targeted Delivery of siRNA to Vaginal Mucosal CD4+ Immune Cells in a Mouse Model

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Purpose: This study aims at developing a pH-sensitive nanomicrobicide for targeted delivery of siRNA to intravaginal CD4+ immune cells as a prophylaxis to prevent intravaginal transmission of HIV. This technology platform consists of antibody-conjugated siRNA nanoparticles (NPs) loaded into a vaginal gel.
Methods: Cy-3 siRNA was condensed by polyethyleneimine and encapsulated into NPs using biodegradable polymer, poly(lactic-co-glycolic acid)-polyethylene glycol. NPs were conjugated to anti-mouse (in vivo)/anti-human (in vitro) anti-CD4 antibody (siRNA-NPs-CD4) or isotype control (IgG) (siRNA-NPs-IgG). Resulting NPs were formulated into 1% hydroxyethyl cellulose (HEC) gel.
Results: NPs had a particle size of 256.0±7.2nm and a zeta-potential of -15.62±1.64mV in PBS (pH7.4) and a particle size of 271.6±1.8nm and a zeta-potential of -8.66±2.43mV in vaginal fluid simulant (VFS, pH4.2). Encapsulation efficiency was 75.6±0.9%. NPs showed a pH-dependent release profile, with sustained release of siRNA in PBS (pH7.4) (~25% over 14 days) and <1% release of siRNA in VFS. siRNA-NPs-CD4 improved siRNA uptake into CD4+ Sup-T1 cells by 72%, 121% and 67% respectively compared to siRNA-NP-IgG, 2hr, 4hr and 6hr post treatment. In vivo studies revealed that the gel formulation improved NP retention in mouse genital tract by one fold compared to NP suspension (without gel), 24hr post intravaginal administration. The 1% HEC gel loading siRNA-

NPs-CD4 improved siRNA uptake into intravaginal CD4+ immune cells by 91% compared to 1% HEC gel loading siRNA-NPs-IgG, 24hr post intravaginal administration. An improvement of 81% in the total siRNA uptake into vaginal tissue was also observed in mice treated with 1% HEC gel loading siRNA-NPs-CD4 compared to mice treated with 1% HEC gel loading siRNA-NPs-IgG, 24hr post administration.

Conclusions: We developed a pH-responsive nanomicrobicide that achieved targeted delivery of siRNA to intravaginal CD4+ immune cells in mice. NPs had desirable particle size and zeta potential for intravaginal delivery and a pH-dependent release profile that preserved siRNA under acidic environments. By formulating into a gel dosage-form, the nanomicrobicide improved retention within the female genital tract and provided ease in administration.

77. Thermo-reversible Gels Based on Triblock Copolymers of PEG and Functionalized Caprolactone: The Effect of Polymer Polydispersity on their Gelation Behaviour

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Purpose: The long term objective of this study is to develop biodegradable stimuli-responsive gels with optimal properties for depot and smart drug delivery. In this study, we first developed an optimum method of solution polymerization for the preparation of block copolymers based on poly(ethylene glycol) (PEG) and functionlaized poly(caprolactone) (PCL). We then investigated the effect of polymer polydispersity on the gelation of triblock copolymers prepared by bulk versus solution polymerization.

Methods: Triblock copolymers of poly(α-carboxyl-co-benzyl carboxylate-ε-caprolactone)-*b*-PEG-*b*-poly(α-carboxyl-co-benzyl carboxylate-ε-caprolactone) (PCBCL-PEG-PCBCL) were prepared through ring opening polymerization of α-benzyl-ε-caprolacton (BCL) and PEG (1450 kDa) by either bulk polymerization or an optimized solution polymerization method using biphenyl as solvent; followed by hydrogenation of block copolymer. Prepared block copolymers were characterized for their molecular weight, polydispersity index (PDI) and branching by ^{1}H NMR and gel permeation chromatography (GPC). The sol-gel transition of polymer solutions in water was measured using inverse flow method, differential scanning calorimetry *(* DSC *)* and rheometrical analysis.

Results: Optimum condition for the synthesis of triblock copolymers of maximum yield and desired degree of polymerization for the PCBCL block (~14) was achieved when 30%wt of biphenyl was used in the reaction. Copolymers with thermo-responsive behavior at 15 % w/w, have shown higher polydispersity and branching; irrespective of the applied method of polymerization. For these block copolymers at 15 % w/w, the sol-gel transition temperature was 35 °C as measured by inverse flow method, DSC and rheometrical analysis.

Conclusion: The present study illustrates successful use of solution polymerization for the preparation of triblock copolymers based on PEG and functionalized PCL. We also demonstrated that the PDI of block copolymers can affect their sol-gel transition. Tri block copolymers with a broader molecular weight distribution, showed better sol-gel transition.

78. Derivation and Experimental Validation of Ion-Exchange Model for Loading Anionic Drugs into Cationic Polyacrylate Polymer Eudragit® RS/RL Films

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Purpose: Cationic polyacrylate polymers, Eudragit® RS and Eudragit® RL (RS/RL), are widely applied as coating materials for making controlled release dosage forms. Due to drug interaction with the cationic quaternary ammonium groups of the polymers, the current diffusion-controlled drug release model is not suitable for describing the loading and release kinetics of anionic drugs in RS/RL-coated dosage forms. Therefore, the aim of this study is to establish a mathematical model to predict loading kinetics of anionic drug into RS/RL films.

Method: A mathematical model combining ion-exchange and diffusion terms was developed to describe the fractional absorption (M_t/M_0) over time, where M_t is the amount of drug remaining in the

external volume at any time and M_0 is the initial amount of drug in the external drug solution. The model was verified using theoretical solutions and then validated by experiments. Solutions of ibuprofen Na or diclofenac Na were incubated with RS/RL polymer films and concentration was monitored by spectrophotometry. Effects of model parameters on drug loading kinetics were analyzed with computer simulations and experiments in triplicates.

Results: All M_t/M_0 curves exhibited gradual decline and reached the equilibrium plateau around 48 h. The model predicted M_t/M_0 profiles matched well with the experimental curves as evidenced by small root-mean-square deviation (<0.0782). Model parameters, e.g. equilibrium binding constant and diffusivity of the drugs in the polymers, were evaluated from the experimental data. Drug loading efficiency and equilibrium loading level were found to depend on external conditions, e.g. solution volume and initial drug concentration. Drug properties appeared to affect loading kinetics.

Conclusion: This work for the first time revealed the effect of interactions between RS/RL and anionic drugs on loading kinetics. The kinetics and thermodynamic parameters determined from this work would be very useful for prediction of release kinetics of RL/RS coated ionic drug-loaded dosage forms.

79. Nano-encapusaltion of Inhibitors of Polynucleotide Kinase/Phosphatase (PNKP) by Polymeric Micelles for Selective Sensitization of Cancer Cells to DNA Damage

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Purpose: The aim of this project is to enhance the outcome of radio and chemotherapy with DNA damaging agents in solid tumors through development of tumor targted delivery systems for inhibitors of important DNA repair enzyme, polynucleotide kinase/phosphatase (PNKP).

Methods: A library of polysubstituted imidopiperidine compounds, were screened for their PNKP inhibitory activity using a novel assay that prevents release of fluorescent 2-aminopurine deoxyribose phosphate from a hairpin oligonucleotide if PNKP phosphatase is inhibited. Identified hit compounds with potent PNKP inhbitory activity were used for encapuslation in polymeric micelles of different structures. The encapsulated drug levels were measured using HPLC and the cumulative *in vitro* release was investigated by a dialysis method. The non-specific toxicity of the PNKP inhibitors was tested against HCT 116 cells using MTS assay. Free and encapsulated drugs were also tested for their activity in sensitization of HCT 116 cells to irinotecan or radiation.

Results: Our fluorescent based assay identified three hit compounds namely A12B4C5, A12B4C60 and A12B4C61 as potent inhibitors of PNKP with Kd values of 0.13 and 0.16 µM, respectively. Efficient loading of A12B4C5, A12B4C60 and A12B4C61 was achieved in polymeric micelles, which showed drug: polymer w/w ratios of 1:40. We also measured 57.7, 63.4, 66.2 % drug release from polymeric micellar formulations of A12B4C5, A12B4C60 and A12B4C61 within 24 h. The potent inhibitors show slight toxicity at doses higher than 20 µM. PNKP inhibitors were able to radio/chemosensitize HCT 116 cells.

Conclusions: Our results point to a potential for encapuslated inhbitors of PKNP for sensitization of colon tumors to DNA damaging chemotherapy and radiation.

80. Development of Anti-CD20 Immuno-micelles for Active Drug Targeting to Hematological Cancer

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Purpose: The aim of this study was to covalently attach the anti CD20 antibody, rituximab, to the surface of the polymeric micelles and assess the effectiveness of this approach in enhancing micellar specific interaction with target cells overexpressing CD20.

Methods: Rituximab, was coupled to Cy5.5 NHS ester at pH=8. The Cy5.5 conjugated antibody was coupled to 3-(N-succinimidyloxyglutaryl) aminopropyl, polyethyleneglycol-carbamyl distearoylphosphatidyl-ethanolamine (NHS-PEG-DSPE). Cy3-N_3^+ was covalently conjugated to a

tribockcopolymer, methoxy poly(ethylene glycol)-b-poly(ε-caprolactone)-b-poly(α-propargyl carboxylate-ε-caprolactone) (MPEG-PCL-PPCL),through click reaction. Mixed micelles were then prepared by incubating Cy5.5 labeled antibody modified PEG-DSPE with MPEG-PCL-PPCL-Cy3 at 1:1 molar ratio overnight. Size, critical micellar concentration (CMC) and kinetic stability of mixed micelles (without any cy3 or cy5.5 probes) were measured by zetasizer (DLS measurement) and compared to that for micelles from the individual polymers. The size and morphology of micelles was also investigated by TEM. Flowcytometry was used to follow the association of plain versus antibody modified mixed micelles with CD20 over expressing PTLD cells using fluorescence at 570 and 707 nm, for Cy3 and Cy5.5, respectively.

Results: The formation of mixed micelles was confirmed by DLS by detecting one peak around 65nm for mixed micelles compared to two separate peaks around 50.4 and 23.1 nm for micelles of individual polymers. Similar results were also found by TEM. The CMC of the mixed micelle was 7.8μg/mL; significantly lower than that of NHS-PEG-DSPE micelle (35.6 μg/mL), and higher than that of MPEG-PCL micelle (3.05 μg/mL). Kinetic stability of the mixed micelle was not significantly different from the MPEG-PCL micelle; however it was significantly higher than that of the NHS-PEG-DSPE micelles. Flowcytometry showed higher association of anti-CD20 micelles with PTLD cells compared to plain micelles and CD20 negative cells (SUP-M2).

Conclusion: The results points to the effectiveness of PEG-DSPE/ MPEG-PCL mixed immune micelles modified on their surface with rituximab in enhancing their association with CD20 overexpressing cells.

81. Delivering *in situ*-Gelling Hydrogels for Ophthalmic Drug Therapies Using a Microinjection Device

Scott B. Campbell, Jun Yang, Ben Muirhead, Heather Sheardown, P. Ravi Selvaganapathy, and Todd R. Hoare

Purpose: Numerous posterior segment ocular diseases are regularly treated via intraocular injections, but the frequency of injections required for these treatments increases the risk of complications. Mixing-induced two-component hydrogels (MITCH) that crosslink *in situ* upon injection via a rapid chemical reaction between two functionalized polymers offer a potential solution, as they can be designed to be transparent, degradable, and enable long-term, sustained drug release. However, in order to assess the *in vivo* capabilities of these hydrogels, very small volumes of each reactive component (1–20 μL) must be injected and no suitable system exists for the administration of MITCH hydrogels at low volumes.

Methods: We have developed a microinjection device that is capable of mixing two reactive precursor polymers for MITCH hydrogels and precisely inject volumes of 1-20 μL through a narrow capillary suitable for ophthalmic therapies. The device involves a double-barrel syringe connected to two inlets of the microfluidic chip, a channel with herringbone mixing grooves, and a volume control reservoir (1-20 μL) with a one-way valve connected to second syringe that pushes the mixed polymer solutions out the capillary.

Results: The device is capable of ejecting hydrogel droplets of controlled volumes (~±15%) in the range of interest (1–20 μL) via a handheld operation into various materials, including bovine vitreous humour at 37°C. *In vivo* experiments involving the injection of fluorescently-labelled poly(oligoethylene glycol methacrylate) (POEGMA) MITCH hydrogels, crosslinked via hydrazide and aldehyde chemistry that react to form degradable hydrazone crosslinks, into the eyes of Sprague Dawley rats showed no significant toxicity relative to controls. Experiments showing the release of fluorescently-tagged model drugs will be performed.

Conclusions: Precisely controlled amounts of in situ-gelling MITCH hydrogels were injected *in vivo* into using a newly-developed microinjection device. Such a system could clinically exploit the favorable properties of injectable hydrogels as ocular drug delivery materials.

82. A Gadolinium-Doxorubicin Nanocomplex as a Novel Targeted Drug-Delivery System

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Purpose: Anthracycline antibiotics, such as

doxorubicin, can form complexes with transition metals. Gadolinium as one of those transition metals has been well investigated as a promising T1 contrast agent for clinical magnetic resonance imaging (MRI). The objectives of this study were to establish a reliable method for fabricating doxorubicin loaded gadolinium nanoparticles and examine the feasibility of this synthesized nanoparticles for delivering the antibiotic doxorubicin into human breast cancer MDA-MB-231 cells and having anticancer efficacy subsequently.

Methods: Doxorubicin loaded gadolinium nanoparticles were fabricated by a simple one-step homogeneous precipitation method. Synthesized nanoparticles were further characterized by means of transmission and scanning electron microscope, dynamic light scattering method as well. Confocal fluorescence microscope was used to visualize the cellular uptake of the nanoparticles by MBA-MD-231 cells after 24 hours' incubation. Flowcytometry experiments were carried out to evaluate the percentage of apoptotic cells after 3-day incubation, and APC-Annexin V was used as the fluorescence dye.

Results: The synthesized doxorubicin loaded nanoparticles possess desirable morphology (sphere), diameters (average size about 150nm) and zeta potential (+13.8 mV). A high doxorubicin loading amount (10.1%, w/w) was achieved. Confocal micrographs show our nanoparticles were actively taken up via endocytosis by MDA-MB-231 human breast cancer cells. A dose-dependent trend in the percentage of apoptotic cells of nanoparticles treated groups was detected by flowcytometry assay.

Conclusion: A novel doxorubicin loaded spherical gadolinium nanoparticle system was developed with good cellular uptake profile and promising therapeutic efficacy. Gadolinium based nanoparticles and chelates were reported as T1 contrast agent for clinical MRI, which means our doxorubicin gadolinium nanoparticles have a great potential for working as a multifunctional platform and personalized medicines.

83. First Report of an Intravesical Therapy with Activity in a Muscle Invasive Bladder Cancer Xenograft Model

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Purpose: We have developed a functionalized nanoparticle formulation of docetaxel to improve treatment outcomes of intravesical chemotherapy. Based on hyperbranched polyglycerol (HPG) technology, our new formulation STK-01: a) solubilises the drug without micelle forming surfactants b) is mucoadhesive, to prolong drug residence time, c) enhances drug uptake into the bladder wall d) has demonstrated safety in preclinical models, and e) has shown promising efficacy in treating non-muscle invasive bladder tumors. The objective of this study was to investigate the effectiveness of STK-01 in a new mouse model of muscle invasive bladder cancer.

Methods: Mice were inoculated with UM-UC3-luc using ultrasound-guided intramural injection and tumor growth was measured by bioluminescence imaging twice a week. On day 8 post-tumor inoculation, mice with established muscle invasive bladder tumors were grouped into 3 treatment groups and were instilled with 50 µL of PBS (control), or 50 µg of docetaxel in Polysorbate 80 (Taxotere), or 50 µg of docetaxel formulated in HPG nanoparticles (STK-01).

Results: All mice developed bladder tumors and the success of tumor implantation was confirmed by bioluminescence and ultrasound imaging. Intravesical therapy with STK-01 significantly ($p<0.001$) inhibited tumor growth compared to the Taxotere treatment group. There was also a significant difference in tumor growth between the STK-01 treated group and the PBS control group. There was no significant difference between the Taxotere treated group and the PBS control group.

Conclusion: A novel formulation of docetaxel (STK-01) was found to be safe and effective when given intravesically to treat muscle invasive tumors in mice. To our knowledge, this is a first report of an

intravesical therapy showing activity in a muscle-invasive bladder cancer model. Our data suggest that intravesical chemotherapy with STK-01 may provide a viable bladder-sparing treatment alternative for patients with muscle invasive bladder cancer who are medically unfit for cystectomy.

84. 120 Encapsulation of Docosahexaenoic Acid in Polymer-Lipid Hybrid Nanoparticles Enhance Efficacy of Co-delivered Synergistic Drug Combination in Multidrug Resistant Breast Cancer Cells

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Purpose: Nanoparticles have exhibited enhanced cytotoxicity against multidrug resistant (MDR) cancer cells. However, increased membrane rigidity in some MDR cancer cells impairs drug uptake and endocytosis of nanoparticles, thus reducing the efficacy of chemotherapy. This overlooked MDR mechanism has been observed by our group and others. But the strategy to circumvent this drug delivery barrier has not been fully explored. The present work is aimed to investigate whether encapsulating unsaturated fatty acid docosahexaenoic acid (DHA) together with synergistic doxorubicin and mitomycin C combination in a polymer-lipid hybrid nanoparticle (DMPLN-DHA) would enhance drug uptake and cytotoxicity of DMPLN without DHA in MDR breast cancer cells.
Method: Both DMPLN and DMPLN-DHA were formulated using oil-in-water simultaneous self-assembly process. Clonogenic assay was used to determine the cytotoxicity of free drug combinations, DMPLN and DMPLN-DHA against both drug sensitive EMT6/WT and MDR EMT6/AR1 murine breast cancer cells. Intracellular localization of DOX after 4 h treatment with free drug cocktails and PLN formulations with and without DHA were visualized under a fluorescence microscopy at λ_{em} 488 nm/λ_{ex} 588 nm. The cellular DOX fluorescence was quantitated by *Image J*.
Results: Compared to DMPLN, DMPLN-DHA significantly enhanced cytotoxicity in both EMT6/WT and EMT/AR1 cells. At low drug concentrations (0.1-1 μM), DMPLN-DHA achieved as high as 91% and 66% cell kill in EMT6/WT and MDR EMT6/AR1 cells, respectively, in contrast to DMPLN with 28% and 0% cell kill in ETM6/WT and EMT6/AR1. Moreover, DMPLN showed only comparable DOX uptake to free drug cocktails, whereas DMPLN-DHA exhibited nearly 3- and 5-fold higher cellular DOX uptake with strong DOX fluorescence signal co-localized with nuclei stained by DAPI in EMT/WT and EMT6/AR1 cells, respectively.
Conclusion: The DHA-containing PLN system provides a novel strategy to enhance intracellular drug delivery across the rigid plasma membrane in MDR cancer cells for improved nanomedicine chemotherapy.

85. Polymer-Lipid Based Nanomedicine of Synergistic Drug Combination for Improving Chemotherapy of Multidrug Resistant Breast Cancer

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Purpose: Chemotherapy is a primary treatment modality for metastatic cancer. However, the development of multidrug resistance (MDR) limits the efficacy of chemotherapy. Drug combination regimens that target multiple cellular mechanisms of MDR are frequently used in the clinic to enhance cancer chemotherapy. Unfortunately, dissimilar pharmacokinetics and tissue disposition of different drugs in free solution compromise the therapeutic effectiveness of combination therapy and increase normal tissue toxicity. The aim of this study is to evaluate polymer-lipid hybrid nanoparticles (PLN) as an emerging nanoparticle system for spatiotemporal co-delivery of synergistic drug combination to tumor tissue and cancer cells for enhanced efficacy in treating MDR breast cancer.
Method: PLN co-loaded with a synergistic ratio of doxorubicin (DOX) and mitomycin-C (MMC) (DMPLN) was formulated using the single-step sonication method followed by oil-in-water simultaneous self-assembly. Intracellular uptake and localization of DOX delivered in various formulations in MDR *EMT6/AR1* breast cancer cells were determined by confocal fluorescence microscopy. Pharmacokinetics and tumor accumulation of DMPLN were evaluated in a murine orthotopic breast tumor model. Tumor

apoptosis was evaluated by immunohistochemical staining of *caspase-3* activation.
Results: DMPLN enhanced intracellular DOX accumulation and localized nuclear distribution compared to free DOX and clinically used *PEGylated* liposomal DOX (PLD, Caelyx®) in MDR cancer cells. Compared to free DOX-MMC cocktail, DMPLN prolonged systemic circulation and co-delivered high concentrations of DOX and MMC at effective ratios into the tumor over at least 24 h. As a result, DMPLN demonstrated higher tumor cell apoptosis compared to the free DOX-MMC combination and PLD (Caelyx®).
Conclusion: DMPLN enabled ratio-metric delivery of synergistic DOX-MMC combination to the tumor site and provided sustained local drug bioavailability to MDR cancer cells. These findings suggest PLN as an efficient platform for nanoscale drug delivery of synergistic drug combination and substantiate the importance of rational design of nanomedicine for improved chemotherapy cocktail.

86. Controlled Delivery System for Highly Soluble Active Ingredients: The Case of Metformin

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Purpose: Despite the huge efforts to formulate highly soluble drugs for controlled delivery, there is still a need of pharmaceutical forms easy to process and using safe excipients. A commercial sustained release form of Metformin is a bilayer system: a swollen Gastro-Retention Dosage Form (GRDF) providing up to 6h retention in stomach and continuous local (stomach and upper intestine) release that may generate a saturable absorption. Our main objective was, using Metformin as drug model, to realize a pharmaceutical device able do deliver highly soluble active principles to the expected absorption windows.
Methods: The excipients of the novel release system were methylcellulose (MC) homogeneously distributed in a calcium-carboxymethylcellulose (CaCMC) dry powders with metformin as model drug. By direct compression, monolithic, coating-free devices have been characterized *in vitro.* An *in vivo* study on beagle dogs was conducted in comparison with an extended-release formulation (Glumetza®).
Results: The size of our dosages in SGF was slightly increased, but then remained stable and the tablet integrity was maintained, suggesting that they will be able to pass through the pylorus into the intestinal tract. The Metformin was released not only in the stomach and upper intestine, but also in the whole intestinal tract including the colon. The liberation patterns in simulated gastric (SGF) and intestinal (SIF) fluids showed the new modified-release tablet forms presented good shape and release kinetics during 2h in SGF and 6h in SIF dissolution. A thick gel formation surrounding the tablet was observed probably contributing to the controlled release of Metformin.
The *in vitro* kinetic profiles and the *in vivo* study showed no marked pharmacokinetic differences between our monolithic metformin formulation with Ca-CMC/MC and the Glumetza® reference.
Conclusion: The new monolithic system can efficiently control the highly soluble metformin. The dry compaction end coating free procedure allows a low cost to manufacture.

Pharmaceutical & Analytical Chemistry

87. Hypoxia-Activated SN-38: Targeting Hypoxic Tumors

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Purpose: Solid tumors are commonly subject to hypoxia because of the inadequate oxygen supply caused by abnormal vasculature and irregular blood perfusion in solid tumors. Hypoxic cancer cells have undesirable properties such as a high tendency to metastasize and resistance to chemotherapy and radiotherapy. An agent against hypoxic cancer cells is thus necessary to hold these malignant cells in check. Hypoxia-activated prodrugs of SN-38 (the active metabolite of Irinotecan) are therefore designed and synthesized to target hypoxic cancer cells.
Methods: The anti-cancer activity of SN-38 can be masked by attaching a substituted benzylic trigger

on SN-38's 10-OH, creating a substituted benzyl-O-SN38 ether. The conversion of the substituent on the benzylic trigger from an electron-withdrawing group (EWG) to an electron-donating group (EDG) (i.e., from EWG-Ph-CH2-O-SN38 to EDG-Ph-CH2-O-SN38) can consequently result in the discharge of SN-38 as the activated anti-cancer agent. In hypoxic tumors, an electron-withdrawing nitro group can be reduced by certain 1-electron reductases to a radical anion in reductive environments only, and can be subsequently reduced to an electron-donating hydroxylamino group; thus nitrobenzyl groups have been selected as the trigger for hypoxia-activated SN-38. Synthetic approaches exploiting a variety of alkylating agents such as mesylates, bromides and alkylating method such as Mitsunobu condition were conducted to synthesize these aforementioned prodrugs.
Results: Nitrobenzyl bromides proved to be the most effective alkylating agents for synthesizing hypoxia-activated SN-38. 4-Nitro and 2-nitro substituted benzyl ethers of SN-38 have been synthesized, with yields of 51% and 74%, respectively.
Conclusion: Two nitrobenzyl alkylated SN-38s have been synthesized successfully, to be tested as hypoxia-activated prodrugs.

88. Development and Validation of a Reverse-phase Liquid Chromatography Mass Spectrometry Method for the Stereoselective Determination of Hydroxyeicosatetraenoic Acids

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Purpose: Hydroxyeicosatetraenoic acids (HETEs) are constitutively produced in vivo by cytochrome P450-mediated hydroxylation of arachidonic acid. HETEs are 11 different regioisomers, 10 of them have a chiral center, leading to 20 different S/R enantiomers. Despite the reported stereoselectivity in the formation and in the biological activities of HETEs, almost all previous studies were confined to the determination of HETEs regioisomers, overlooking HETEs enantiomers. This is because the previously-reported separation of HETEs enantiomers needs normal-phase chromatography and chiral columns after methyl esterification of HETEs. Therefore, the aim of the current work is to develop a reverse-phase liquid chromatography method for the stereoselective determination of HETEs.
Methods: HETEs were esterified at the chiral center with (+)-O,O′-diacetyl-L-tartaric anhydride (DATAAN) to from HETE-DATAAN diastereoisomers. Thereafter, HETE-DATAANs were separated using a gradient elution of water-acetonitrile-methanol-isopropanol-ammonium formate mixture using reverse phase C18 column at 30°C. Both single-ion and multiple-reaction-monitoring (Waters Micromass ZQ 4000 spectrometer and AB Sciex QTRAP 2000) were used under negative ion-mode.
Results: Separation of the S and R enantiomers was achieved for 5-, 8-, 11-, 15-, 16-, 17- and 19-HETEs, but not 9-, 12- and 18-HETEs. Single-ion-monitoring of HETE-DATAANs were performed at m/z=535, and the linearity range extended between 0.0625 and 2 µg/mL. HETE-DATAANs were stable at least 4 weeks, and the intraday and interday precision and accuracy did not exceed 20% of %CV and %error, respectively, at the lower limit of quantitation. Also, 2 specific transitions were determined for each HETE-DATAAN that allowed the simultaneous stereospecific determination of individual HETE by multiple-reaction-monitoring.
Conclusion: The new method is sensitive, reliable and compatible with the readily available liquid chromatography systems that would facilitate correlation studies on HETEs levels with disease state, promoting the discovery of new disease markers and novel drug targets.
Support: This work was funded by CIHR to AOSE, and AAE is the recipient of Alberta Innovates-Health Solutions studentship.

89. Targeting the Oncogenic FOXM1 Transcription Factor in Cancer Treatment

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Purpose: Genome-wide gene expression profiling of human cancers has consistently identified the Forkhead box M1 (FOXM1) transcription factor as one of the most commonly activated genes in cancer cells. Also, abnormal activation of the FOXM1 gene is regarded as one of the hallmarks of chemoresistant

cancer cells. Accumulating evidence suggests that targeted FOXM1 inhibition could be a promising strategy to treat many types of cancer. The aim of this project is to validate the FOXM1 transcription factor as a drug target.

Method: We recently carried out a series of molecular modeling protocols in which we have determined the binding energies of 3,323 FDA-approved drugs within the FOXM1/DNA binding domain and we have identified six promising virtual reference drugs with significant binding affinities. In the lab, the MTT assay has been carried out on HepG-2 cell line to test the ability of the drugs to inhibit cancer cell proliferation, followed by RT-PCR to measure the expression of FOXM1 and its downstream target genes: MMP2, KIF20A, ccnb1, ccnd1, NEK2, VEGFa, SOD2, and BcL2.

Results: Three of the drugs gave promising primary results including: thiostrepton (control) IC50 = 2.293 uM, troglitazone IC50 = 17.76 uM, and gliquidone IC50 = 61.82 uM. As well, they found to inhibit the expression of FOXM1 and its downstream target genes except MMP2 gene for thiostrepton and gliquidone.

Conclusion: We found that the drug troglitazone, a known anti-diabetic agent, exerts strong binding interactions in the FOXM1/DNA binding domain, making this molecule the best drug candidate to inhibit the transcriptional activity of this oncogenic protein

90. Inhibition of Influenza A M2 Ion Channel by Novel, Non-cytotoxic Derivatives of Hexamethylene Amiloride

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Purpose: M2 is a virally-encoded ion channel that is required for influenza replication. Licensed therapies such as amantadine and rimantadine, which are potent M2 inhibitors, are no longer effective due to widespread drug resistance. Almost all adamantane-resistant viruses encode a S31N mutation within M2. Thus, compounds that target both WT and S31N mutant are highly desired. We describe novel HMA-derived compounds that inhibit WT and S31N M2 and viruses with minimal cytotoxicity.

Methods: Conventional medicinal chemistry approaches, molecular docking and dynamics (MD) simulations of drug-M2 interactions supported our design hypothesis. In-house medicinal chemistry was carried out to synthesize derivatives. We investigated M2 activity by co-transfecting cells with plasmids encoding GFP and M2(S31/N31) and recording pH-dependent currents by whole-cell patch clamp electrophysiology. Antiviral activities were tested in a viral cytopathic assa**y.**

Results: The potency of the most active compound (SM111) in inhibiting WT influenza virus is comparable with that of amantadine (EC_{50} = 5.2 µM vs. 0.4 µM) which correlates well with the electrophysiology assay. On the other hand, SM146 shows dual inhibitory effect against both A/M2 WT and the mutant (S31N) with an IC_{50} of 0.6 µM and 4.4 uM respectively. SM146 also inhibited viral replication in viral cytopathic assay with an EC_{50} of 39.6 µM and 18.2 µM against InfluA virus bearing S31 and N31 respectively.

Conclusion: We described a novel class of acylguanidines that inhibit InfluA virus and M2 ion channel and are stable and tolerated *in vivo*. SM146 is the first and the most potent non-adamantane dual inhibitor (S31 and N31) of InfluA virus and M2 ion channel. The potency of the lead molecule in both electrophysiology and antiviral assays suggests efficacy of this novel class of compounds which can act as a basis for their further development as potential broad-spectrum antivirals in attempt to confront InfluA virus resistance.

91. Determination of Polyphenolic Content and Antioxidant Capacity of Wild Newfoundland Berries

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Purpose: Antioxidants including polyphenols and ascorbate found in *Vaccinium* berry species (e.g. blueberries and lingonberries) have been reported to have a positive effect on health, including brain aging. We have conducted a detailed chemical analysis of compounds detected in *Vaccinium* species. We also performed a pilot study aimed at determining the extent to which polyphenols can enter the brain when included in the diet.

Method: Berries were collected from several locations in the St. John's, Newfoundland area, and

extracts were produced using a variety of solvents. Biochemical assays were performed to determine the phenolic content of extracts, including total phenolics, tannins, flavonoids, and antioxidant capacity. Comparisons of ascorbic acid levels between wild lingonberries and blueberries were also determined. To quantify and identify major anthocyanins, High-Performance Liquid Chromatography Mass-Spectroscopy (HPLC-MS) analysis was performed on extracts. Mice were also administered blueberry extracts by oral gavage once a day for two weeks, at which time they were killed and the brains were harvested.

Results: The biochemical assays showed that leaves have a significantly higher content of polyphenols and ascorbate in comparison to fruits. Blueberries also had a higher level of ascorbate present in both the leaf and fruit extract in comparison to wild lingonberries. Using HPLC-MS, more anthocyanins were identified and detected in blueberry fruit extracts than leaves, but the anthocyanins in leaf extracts were present in higher quantity. We were unable to detect polyphenols such as anthocyanins in the brain tissue of mice.

Conclusion: Leaves have a significantly higher level of antioxidants compared to the fruits, suggesting potential use as nutraceutical products. Although we were unable to detect anthocyanins in brain, this was likely due to technical issues and work is still ongoing in order to determine the extent to which polyphenols can enter the brain.

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Pharmacokinetics & Pharmacodynamics

92. The Impact of Diet-induced Obesity on the Metabolism of Amiodarone to Desethylamiodarone

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Purpose: Obesity is widespread throughout the world, and is associated with comorbidities that often require a pharmacological intervention. Here we examined for the functional changes in drug metabolism caused by obesity, using the antiarrhythmic drug amiodarone as a test substrate.

Methods: Livers were harvested from male Sprague–Dawley rats given for 14 weeks either a.) control diet with water, b.) Normal rodent chow and high fructose corn syrup water (HFCS), c.) 45% high fat diet (HFD) chow with water, or d.) a combination of HFCS and HFD. After the isolation of hepatic microsomal proteins, amiodarone HCl was incubated with the microsomes. The incubation mixture consisted of different concentrations of AM, 2 mg/mL microsomal protein, 1 mM NADPH and 5 mM $MgCl_2$ in 0.5 M phosphate buffer (pH=7.4) in a total volume of 0.5 ml. The incubation was performed over the linear range of the formation of the AM metabolite desethylamiodarone (DEA) for 10min at 37°C. Reactions were stopped by the addition of cold acetonitrile followed by HPLC analysis for AM and DEA. The Michaelis-Menten equation was used to determine V_{max} and K_m.

Results: There was a significant reduction in Vmax in the HFD group and increase in Km in HFCS group compared to lean controls. In addition, a significant reduction of CLint in all groups compared to controls.

Conclusion: Obesity can decrease the functional activity of liver drug metabolizing enzymes. If translated to humans this finding might require adjustment of the amiodarone dose in obesity.

Group	Vmax, pmol/mg protein/min	km, μM	CLint, uL/mg/min
Control	150±28.7	59.8±21.6	2.65±0.67
HFD	73.1±6.10[a]	44.3±15.3	1.78±0.53[d]
HFCS	137±21.9	119±12.9[b]	1.15±0.16[d]
HFD-HFCS	136±61.4	101±50.5[c]	1.51±0.50[d]

Comparison were made using one way ANOVA. [a]different from control, HFCS, and HFD-HFCS ($p<0.050$); [b]different from control and HFD ($p<0.050$); [c]different from HFD ($p<0.050$); [d]Different from control.

93. Effect of Diet Induced Obesity on Dronedarone Microsomal Metabolism in the Rat

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Purpose: To explore the effect of diet induced obesity on the metabolism of dronedarone as a substrate.
Methods: Livers were harvested from male Sprague–Dawley rats (n=6) exposed to the following diets for 14 weeks: a.) normal rodent chow and water (controls), b.) 45% high fat (HFD) diet and water, c.) normal rodent chow and high fructose corn syrup water (HFCS), and d.) both HFD and HFCS. The microsomal proteins were isolated and exposed to dronedarone. The incubation mixture consisted of different concentrations of dronedarone, 0.5 mg/mL microsomal protein, 1 mM NADPH and 5 mM $MgCl_2$ in 0.5 M phosphate buffer (pH=7.4) in a a total volume of 0.3 mL. Incubation was performed over the linear range for the dronedarone metabolite (desbutyldronedarone) formation for 10 min at 37°C. HPLC was used to determine the concentration of analytes. Substrate inhibition and Michaelis-Menten equations were used to determine V_{max} and k_m.
Results:

Group	V_{max} , *pmol/mg protein/min*	K_m, *μM*	CL_{int}, *μL/min/ mg protein*
Control	210.8±3.4	6.7±2.5	33.6±9.6
HFD	95.4±17.4†	96.2±41.5†	1.1±0.23†
Data are expressed as mean ± SD.			

The formation of desbutyldronedarone in Controls followed a pattern consistent with substrate inhibition/inactivation (the velocity curve reached the maximum and then descended as the substrate concentration increased further). There were significant difference ($p<0.05$) in V_{max}, K_m and CL_{int} values in HFD group compared to Controls (Student's t-test). In the HFCS and combined HFD-HFCS groups there were linear increases in desbutyldronedarone formation vs. concentration profiles over the span of concentrations studied, preventing an estimation of V_{max} or k_m. However, it was clear that the formation rates were reduced compared to controls based on the concentration vs. rate plots.
Conclusion: This data showed that diet induced obesity causes a decrease in the functional activity of liver microsomes.

94. Using Population PBPK Modelling to Explore Variability in Trastuzumab Pharmacokinetics

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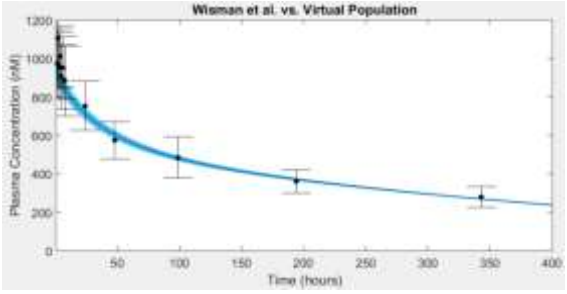
Purpose: The project seeks to explore the effects of anthropometric diversity on the pharmacokinetics of trastuzumab using population PBPK modelling and virtual population generation. The hypothesis is that the interindividual variability in trastuzumab pharmacokinetics can be accounted for by diversity in anthropometric parameters (height, body mass and organ flow rates).
Methods: A comprehensive *in silico* whole-body PBPK model was developed for trastuzumab according to a platform model and optimized using standard modelling methods. A virtual population was generated with diversity in height, body mass and organ flow rates that matched the mean and standard deviation in anthropometric parameters from the sample population in an experimental pharmacokinetic trial (Wisman et al.). All other parameters were held constant between individuals. The virtual human parameters were used as inputs for the model and the simulated variability was compared with the observed variability in the experimental pharmacokinetic trial (Wisman et al.).
Results: The solid blue shading indicates the standard deviation of the plasma concentration values for the virtual population. The black lines mark the standard deviation seen in the trial by Wisman et al.



Conclusion: Anthropometric diversity is responsible for only a small component of the interindividual variability seen in trastuzumab pharmacokinetics. Further research with this model will be conducted to identify the influence of other parameters on

variability. The model and conclusions for trastuzumab can be generalized to all monoclonal antibody drug products.

Acknowledgement: Paul Malik is the recipient of 2016 GSK/CSPS National Undergraduate Student Research Program Award.

95. Anti-cancer Stem Cell Effect and Pharmacokinetics of Composite Polymeric Micelles of Reparixin and Paclitaxel

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Purpose: Breast cancer stem cells (CSCs) were reportedly resistant to conventional therapies, and their proportion increases after treatment. Gene profiling of CSCs revealed overexpression of CXCR1, a receptor for cytokine IL-8. We have developed composite polymeric micelles (PMs) of reparixin (RPX, a potent CXCR1 antagonist) and paclitaxel (PTX) to target both CSCs ($CXCR1^+$ and $ALDHFLUOR^+$) and bulk tumor cells respectively, and tested their anti-CSCs effects *in vitro* and pharmacokinetics *in vivo*.

Methods: Poly(ethylene glycol)-block-poly(D,L-lactic acid) PMs were prepared by lyophilization technique. *In vitro* cytotoxicity was evaluated in sorted ($CXCR1^+$ and $ALDEFLUOR^+$) and unsorted mammosphere HCC-1954 breast cancer cells. Stemness reduction efficacy was evaluated using limited dilution assay (LDA) and mammosphere formation assay (FMA). Pharmacokinetic study was performed in rats intravenously administered with PMs. Plasma drug concentrations were analyzed using validated LC-MS/MS assay. Pharmacokinetic parameters were calculated using non-compartmental model by WinNonlin® software.

Results: Significant decrease in viability was observed in unsorted cells treated with PTX and composite PMs. In sorted $CXCR1^+$ cell RPX-PMs induced significant viability loss, while PTX-micelles induced lower cytotoxicity. Composite PMs efficiently decreased viability in both unsorted and sorted cells. Flow cytometric analysis indicated 3- and 5-fold decrease in $CXCR1^+$ and $ALDHFLUOR^+$ CSCs respectively. The increase confidence interval of 1 CSCs per 250 cells confirmed the decreased stemness of cultures treatment with composite PMs. Plasma elimination half-life ranged 0.94-1.06h for PTX and 0.8-1.07h for RPX in rats. Compared to PTX- or RPX-micelles, composite PMs produced higher AUC for both PTX (13.56±1.80μg*h/ml) and RPX (40.36±4.09μg*h/ml). Composite PMs also increased C_{max} (63.31±19.05μg/ml for PTX and 135.97±19.96μg/ml for RPX) and reduced V_{ss} (0.62±0.32L/kg for PTX and 0.12±0.01L/kg for RPX).

Conclusion: Composite PMs significantly reduced viability and stemness of CSCs in HCC-1954 cancer cells. Pharmacokinetic study in rats indicated enhancement of AUC and C_{max} for both drugs by composite PMs.

96. Optimization and Development of Novel Topical Intestinal Agonists of the Bile Acid Receptor TGR5 for Treatment of Diabetes Mellitus and Associated Metabolic Diseases

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Purpose: TGR5 is a ubiquitous GPCR sensitive to bile acids. Its activation in intestinal enteroendocrine L cells increases GLP-1 secretion, an incretin hormone known to have a good potential in the treatment of diabetes mellitus. Nevertheless, recent *in vivo* experiments have shown that activation of TGR5 by systemic agonists could induce on-target unwanted effects such as swelling of the gallbladder, or cardiovascular dysfunctions. We have hypothesized that selective activation of TGR5 in the intestine combined with limited systemic exposure would lead to beneficial effects on glucose homeostasis, while preventing unwanted effects.

Methods: Using the SAR obtained on our TGR5 agonists, structural elements were introduced to prevent systemic exposure. Such analogs were evaluated *in vitro* to assess their potency on TGR5. Solubility, LogD, microsomal stability and Caco2 permeability were also determined. *In vivo* experiments were then carried out on mice to study the pharmacokinetic and pharmacological profiles of one of the best compound.

Results: Introduction of a sulfonate group on an adequate position through a convergent 10 steps

synthesis lead to compound **2**. It displayed promising improvements in physico-chemical and ADME properties compared to its unmodified analog compound **1** (Log D : 0.8 vs 3.5 ; Caco2 permeability : 0.03 10^{-6} cm/s vs 4.4 10^{-6} cm/s), while remaining as potent (mEC_{50} : 0.5 nM vs 0.8 nM). Oral administration of **2** in mice lead to a 10,000 fold difference between intestinal and plasmatic concentrations ($C_{max\ int.}$ = 900 µM vs $C_{max\ pl}$ = 0.1 µM). Unexpectedly, gallbladder concentrations were found to be 100 fold higher than in the plasma ($C_{max\ GB}$ = 10 µM). Dose-dependent and time-dependent evaluation of pharmacological effects established the proof of principle that it was possible to trigger an enhanced GLP-1 secretion (6.1 fold) with no significant gallbladder swelling.

Conclusion: Our strategy lead to compound **2**, a potent agonist of TGR5 with a fine-tuned PK profile, translating into an optimized pharmacological behavior *in vivo*. This compound will now be further evaluated in animal models of diabetes mellitus.

Note: Part of this work was already presented at the 18th SCI/RSC Medicinal Chemistry Symposium in Cambridge, UK (Sunday 13 - Wednesday 16 September 2015)

AFPC POSTER PRESENTATIONS - JUNE 2, 2016

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AFPC - 35	Shawn Bugden, ***I fan Kuo***	Enhancing Quality by Using Instruction on Qualitative Methods as a Course Evaluation Tool
AFPC - 36	Grace Frankel, Christopher Louizos, ***I fan Kuo***	New Skills Lab Component for Pharmacy Student: Ordering and Interpreting Laboratory Tests
AFPC - 37	***Vaughn T. Chauvin***, Tamiz Kanji	The Impact of Practical Skills Instruction and Application in Improving Student Confidence to Engage in Point of Care INR Monitoring and Management
AFPC - 38	***Annie Lee***, Andrew Tolmie, Mahmoud Suleiman, Diana Spizzirri, Stephanie Chiu, Henry Halapy	Designing, Testing and Implementing a Standard Assessment Tool for Field-Based Pharmacy Training
AFPC - 39	***Annie Lee***, Thomas Huang, Danish Tanwar, Certina Ho	Effectiveness of the Peer-to-Peer Mentoring Model for Transitioning from Classroom to Professional Practice
AFPC - 40	***Christopher Louizos***, Casey L. Sayre, Bruce D. Audit, Grace E. Frankel, Robert D. Renaud	Implementing the Informatics for Pharmacy Students E-resource into the University of Manitoba, College of Pharmacy
AFPC - 41	***Glenda P. MacDonald***, Peter S. Loewen, Patricia Gerber, Madeleine H.P. Lee, James P. McCormack	Brain Gain: Evaluation of Prior Learning Assessment and Recognition (PLAR) in a Canadian Doctor of Pharmacy Program
AFPC - 42	***Rachel Magarinos-Torres***, Milton D. Lucas-Filho, Monique A. Brito	Profile of the Hospital Pharmacists Workers in Rio de Janeiro, Brazil
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AFPC - 55	Neelam Dhaliwal, ***Frances Simpson***, Ashley Shaw, Angela Kim-Sing	Developing Online Learning Modules for Pharmacy Practice Educators
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