13th Canadian Society for Pharmaceutical Sciences (CSPS) Annual Meeting

Held jointly with AFPC
First Annual Canadian Pharmacy Education and Research Conference (CPERC)

June 2-5, 2010
River Rock Casino Resort
Vancouver, BC, Canada

International Symposium on Pharmacy & Pharmaceutical Sciences:

New Frontiers in Pharmaceutical Sciences

Organizing Committee

Chair
Laszlo Endrenyi, University of Toronto, Toronto, ON

Scientific Chairs
Robert Young, Simon Fraser University, Burnaby, ON
Christine Allen, University of Toronto, Toronto, ON

Local Organizing Committee
David Kwok, BRI/BRIVAL Inc., Vancouver, BC
Frank Abbott, AFPC, Vancouver, BC
Athena Juneson, Vancouver, BC
Dave Marchand, UBC, Vancouver, BC

Cover design: Special thanks to Sam Gilchrist, Seabass Studios Photography/Scientific Illustration, Vancouver (http://seabass.smugmug.com/). Sam is currently a Ph.D. candidate at UBC and is attending the Symposium.

Symposium 2010 Awards

CSPS Award of Leadership in Canadian Pharmaceutical Sciences:

Co-Recipient: Ms. Anne Tomalin, President, i3 CanReg Inc., Dundas, ON
Co-Recipient: Dr. Pieter Cullis, Professor, Biochemistry & Molecular Biology, University of British Columbia/CDRD, Vancouver, BC

GlaxoSmithKline/CSPS Early Career Award:

Recipient: Dr. Carolyn Cummins, Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, ON

Fellow Award:

Recipient: Dr. Robert Young, Simon Fraser University, Burnaby, BC

Gattefossé Canada/CSPS Lipid-Based Drug Delivery Award

Co-Recipient: Aws Alshamsan, University of Alberta
For his paper entitled: "The Induction of tumor apoptosis in B16 Melanoma Following STAT3 siRNA Delivery With a Lipid-Substituted Polyethylenimine", by Aws Alshamsan, Samar Hamdy, John Samuel, Ayman O.S. El-Kadi, Afsaneh Lavansanifar and Hasan Uludag.
Published in *Biomaterials* 31 (2010) 1420–1428.
Co-Recipient: Loan Huynh, University of Toronto
For her paper entitled: "Enhancement of Docetaxel Solubility via Conjugation of Formulation-Compatible Moieties, by Loan Huynh, Jean-Christophe Leroux and Christine Allen.
Published in *Org. Biomol. Chem*. 2009, 7, 3437–3446.

Poster Awards - Winners to be announced at the Symposium Gala Dinner:

- **Antoine A. Noujaim Award of Excellence**
- **Biovail Contract Research Award of Excellence**
- **Cedarlane Award of Excellence**

2010 National Summer Student Research Program Sponsored by Merck-Frosst Canada Ltd.

National Directors:	Dr. Kishor M. Wasan (University of British Columbia) Dr. Dale Meisner (Merck-Frosst Canada Ltd.)
Elissa Aeng	University of British Columbia (Supervisor: Dr. Helen Burt)
Title of Project:	Micellar Paclitaxel and Docetaxel for Intravesical Bladder Cancer Therapy
David Nguyen	University of Manitoba (Supervisor: Dr. Frank Burczynski)
Title of Project:	Cellular Antioxidant Effect of Diltiazem and Silymarin
Sarai Hamodat	Memorial University of Newfoundland (Supervisor: Dr. John Weber)
Title of Project:	Analyzing the potential neuroprotective effects of native Newfoundland and Labrador berries
Corey Ramer	University of Alberta (Supervisor: Dr. Paul Jurasz)
Title of Project:	A Novel Anti-Angiogenesis Mechanism of Angiostatin: Inhibition of Endothelial Cell MMP-2 Production
Jenna McNeil	Dalhousie University (Supervisor: Dr. Kerry Goralski)
Title of Project:	Characterization of P-glycoprotein transport in a novel human proximal tubule cell line
Lindsay Wong	University of Toronto (Supervisor: Dr. Suzanne Cadarette)
Title of Project:	Confounding in Pharmacoepidemiologic Studies of Fracture Risk
Katherine Lang	University of Saskatchewan (Supervisor: Dr. Anas El-Aneed)
Title of Project:	Qualitative Investigation of Barriers to Accessing Health Services by Injection Drug Users in Saskatoon Health Region

CSPS Conference Program

New Frontiers in Pharmaceutical Sciences

Wednesday, June 2, 2010

3:30-7:00 PM	**Registration** (CSPS & CPERC Desks - Lower Theatre Lobby)
5:30-7:00 PM	**Welcome Wine and Cheese Reception - Joint CSPS & AFPC** (Upper Theatre Lobby) Exhibition Opens. **(SPONSORED BY CONTROLLED RELEASE SOCIETY-CANADIAN CHAPTER)**

Thursday, June 3, 2010

Continental Breakfast in Exhibit area (Upper Theatre Lobby)
7:30 AM **Registration** (Lower Theatre Lobby)
8:00 AM - 6:00 PM **Poster Presentations** (Upper and Lower Theatre Lobbies)

8:30	**PLENARY SESSION** (Whistler Ballroom A&B) Chair: Laszlo Endrenyi, University of Toronto. Toronto, ON **(SESSION SPONSORED BY FMC BIOPOLYMER)**	
	Keynote Speaker: Pieter Cullis, University of British Columbia/CDRD, Vancouver, BC "**Lipid-Based Nanomedicines: Applications to Conventional Drugs and Genetic Drugs**"	
9:30-10:00	Poster Viewing and Break	
10:00-12:30	**Session I a** (Whistler Ballroom A)	**Session I b** (Whistler Ballroom B)
	PRODRUGS AS NOVEL THERAPIES Chair: Robert Young, Simon Fraser University, Burnaby, BC	**NEW ADVANCES IN DRUG METABOLISM AND DISPOSITION: GENETIC VERSUS ENVIRONMENTAL INFLUENCES** Chair: Micheline Piquette-Miller, University of Toronto, Toronto, ON
10:00-10:40	**PEG-based Prodrugs Improve the Anticancer Activity of Small Molecule Cytotoxics** Hong Zhao, Enzon Pharmaceuticals, Piscataway, NJ	**Altered Drug Metabolism and Transport in Cancer and Cachexia** Graham Robertson, University of Sydney, ANZAC Research Institute, Sydney, Australia
10:40-11:20	**Role of Prodrug Design in Lead Optimization Strategy** Reza Oliyai, Gilead Sciences, Foster City, CA	**Pharmacogenomics of Drug Disposition: Theory and Application** Anahita Bhathena, Abbott Laboratories, Abbott Park, IL
11:20-11:50	**Development of a Weak-Base Docetaxel Derivative That Can be Loaded into Liposomal Nanoparticles** Norbert Maurer, Centre for Drug Research & Development, Vancouver, BC	**Genetic and Environmental Regulation of Drug Metabolizing Enzymes and Transporters by Nuclear Receptors** Wen Xie, University of Pittsburgh, Pittsburgh, PA

11:50-12:10	**Novel Bone-targeting Prostaglandin EP4 Receptor Agonist-Bisphosphonate Pro-drug Conjugates as Dual Action Therapies for Treatment and Reversal of the Effects of Osteoporosis** Robert Young, Simon Fraser University, Burnaby, BC	**Regulation of Drug Transporters and its Impact on Drug Response and Kinetics** Micheline Piquette-Miller, University of Toronto, Toronto, ON
12:10-12:20 12:20-12:30	**Trainee presentations:** **-Non-ulcerogenic Effective Non-steroidal Anti-inflammatory Prodrugs of Aspirin, Ibuprofen, and Indomethacin: Is Nitric Oxide-release Required?** Sarthak Jain, University of Alberta, Edmonton, AB **-Bone-targeting Salmon Calcitonin Analogue: Synthesis, Characterization and *in vivo* Evaluation** Krishna Hari Bhandari, University of Alberta, Edmonton, AB	**Trainee presentations:** **-The Effect of Nrf2 Knockout on the Constitutive Expression of Drug Metabolizing Enzymes in C57Bl/6 Mice Livers** Anwar Anwar-Mohamed, University of Alberta, Edmonton, AB **-Naturally Occurring Variants of Human Aldo-keto Reductases Alter in vitro Metabolism of Doxorubicin and Daunorubicin** Onkar S. Bains, University of British Columbia, Vancouver, BC
12:40-2:00	**Luncheon and CSPS Annual General Meeting** - (Theatre) Poster viewing	
12:40-2:00	AFPC/CSPS Trainee Luncheon Session – **Wayfinding in the Pharmaceutical Sciences: Challenges & Rewards of an Academic Career** (Capilano & Birkenhead Rooms)	
2:00-5:00	**Session II a** (Whistler Ballroom A)	**Session II b** (Whistler Ballroom B)
	NEW DIRECTIONS IN CLINICAL APPLICATIONS OF DELIVERY SYSTEMS FOR CANCER TREATMENT AND DIAGNOSIS Chair: Afsaneh Lavasanifar, University of Alberta, Edmonton, AB Co-Chair: Christine Allen, University of Toronto, Toronto, ON **(SESSION SPONSORED BY BAYER)**	**BIOMARKERS (FOR PRECLINICAL DEVELOPMENT, TOXICOLOGY, CLINICAL TRIALS)** Chair: Bruce McManus, PROOF Centre of Excellence, Vancouver, BC
2:00-2:30	**Opportunities for Combination Medical Devices in Local siRNA Delivery and Therapeutics** David Grainger, University of Utah, Salt Lake City, UT	**What Pharma Needs with Respect to Biomarkers – COPD as an Example** Bruce Miller, GlaxoSmithKline, King of Prussia, PA
2:30-3:00	**Polymeric Micelles for Combinatorial Drug Delivery** Glen Kwon, University of Wisconsin, Madison, WI	**What the Diagnostic Industry Can Offer** Mike Pintek, Luminex Corporation, Austin, TX
3:00-3:30	Poster Viewing and Break	
3:30-4:00	**Nanotechnology Applications in Cancer Diagnosis and Therapy** Mansoor Amiji, Nanomedicine Education and Research Consortium, Northeastern University, Boston, MA	**Biomarkers in Transplantation: From Purpose to Discovery and Validation of Signatures of Immune Rejection** Bruce McManus, PROOF Centre of Excellence, Vancouver, BC
4:00-4:30	**Targeted Nano-therapeutics for the Treatment of Resistant Cancers** Afsaneh Lavasanifar, University of Alberta, Edmonton, AB	**Bringing the Community Together for Efficient Biomarker Strategies** Shawnmarie Mayrand-Chung, The Biomarkers Consortium, National Institutes of Health, Bethesda, MD

4:30-4:40	**Trainee presentations:** **-Enhancement of Docetaxel Solubility via Conjugation of Formulation-Compatible Moieties** Loan Huynh (Co-winner of Gattefossé Award), University of Toronto, Toronto, ON	**Trainee presentations:** **Disease-drug interaction: Reduces Response to Verapamil Despite Increased Concentration in Active Crohn's Disease** Forough Sanaee, University of Alberta, Edmonton, AB
4:40-4:50	**-Design and Development of a New Family of Self-assembling Gene Delivery Nanoparticles using Cationic Amino Acid Substituted Gemini Surfactants** Jagbir Singh, University of Saskatchewan, Saskatoon, SK	**Inflammation Downregulates Angiotensin Converting Enzyme 2 in Rat Heart** Sherif Hanafy, University of Alberta, Edmonton, AB
5:00 - 6:00	Reception & Poster Viewing - Joint CSPS/AFPC (Theatre Upper Floor Foyer) **(RECEPTION SPONSORED BY MERCK)**	

Friday, June 4, 2010		
Continental Breakfast in Exhibit area (Upper Theatre Lobby) 8:00 AM **Registration** 8:00 AM - 4:00 PM **Poster Presentations** (Upper and Lower Theatre Lobbies)		
7:00 - 8:20	**CSPS/AFPC Trainee Breakfast Session: Career Mentoring** (Chairman's Room)	
8:30-9:40	**SESSION III** (Whistler Ballroom A & B) **AWARD WINNER PRESENTATIONS** Chair: Elizabeth Vadas, InSciTech Inc., Dorval, QC	
	CSPS Leadership Award - Anne Tomalin, i3 CanReg Inc., Dundas, ON **"CanReg: The Successful Convergence of Government, Academia and Industry"** **CSPS Leadership Award** - Pieter Cullis, University of BC/CDRD, Vancouver, BC: **"Adventures of a Serial Entrepreneur"** **GlaxoSmithKline Early Career Award** - Carolyn Cummins, University of Toronto **"The Liver X Receptors in the Regulation of Cholesterol and Glucose Metabolism"**	
9:40-10:00	Poster Viewing and Break	
10:00-12:20	**Session IV a** (Whistler Ballroom A)	**Session IV b** (Whistler Ballroom B)
	siRNA AS *IN VIVO* THERAPEUTICS Chair: Pieter Cullis, University of British Columbia/CDRD, Vancouver, BC **(SESSION SPONSORED BY MERCK)**	**ROLE OF LIPIDS IN MODIFYING ORAL AND PARENTERAL DRUG DELIVERY** Chair: Kishor Wasan University of British Columbia, Vancouver, BC Co-Chair: Dion Brocks, University of Alberta, Edmonton, AB
10:00-10:30	**Small Interfering RNA as a Therapeutic Modality** Alan Sachs, Merck Research Laboratories/Sirna Therapeutics, San Francisco, CA	**Lipid Based Formulations of Anticancer Drugs: What's In and What's Out** Marcel Bally, BC Cancer Agency, Vancouver, BC
10:30-11:00	**Progress in the Development Delivery Systems for siRNA** Mark Tracy, Alnylam Pharmaceuticals, Boston, MA	**Lymphatic Transport of Drugs** Chris Porter, Monash Institute of Pharmaceutical Sciences, Parkville, Australia
11:00-11:30	**Membrane/Core Type Nanoparticles for Co-delivery of siRNA and Doxorubicin** Leaf Huang, University of North Carolina at Chapel Hill, Chapel Hill, NC	**Role of Lipids and Lipoproteins in Modifying the Pharmacokinetics and Tissue Distribution of Hydrophobic Drugs** Dion Brocks, University of Alberta, Edmonton, AB

11:30-12:00	**Ionizable Cationic Lipids and In Vivo Delivery of siRNA: How Low Can We Go?** Michael Hope, AlCana Technologies, Vancouver, BC	**Engineered Lipid-Based Nanoparticles and Nanocapsules for Overcoming Multi-Drug Resistance in Cancer** Russell Mumper, University of North Carolina at Chapel Hill, Chapel Hill, NC
12:00-12:10	**Trainee presentation:** **The Induction of tumor apoptosis in B16 Melanoma Following STAT3 siRNA Delivery With a Lipid-Substituted Polyethylenimine** Aws Alshamsan (Co-winner Gattefossé Award), University of Alberta, Edmonton, AB	**Trainee presentation:** **Synthesis and *in vitro* Evaluation of Peptide Decorated Polymeric Micelles for Paclitaxel Delivery to Human Cancer Cells** Mostafa Shahin, University of Alberta, Edmonton, AB
12:20	Lunch & Poster Viewing (Upper and Lower Theatre Lobby)	
1:30-4:30	**Session V a** (Whistler Ballroom A)	**Session V b** (Whistler Ballroom B)
	CLINICAL DEVELOPMENT OF NANOMEDICINES Chair: Lawrence Mayer, Celator Pharmaceuticals Corp., Vancouver, BC Co-Chair: Ron Boch, Variation Biotechnologies Inc., Ottawa, ON	**TECHNICAL AND REGULATORY ISSUES FOR THE BIOANALYTICAL LABORATORY** Chair: Athena Juneson, Vancouver, BC Co-Chair: David Kwok, BRI Biopharmaceutical Research Inc., Vancouver, BC
1:30-2:00	**Navigating the Path to Approval with Nanomedicines: Challenges and Opportunities** Lawrence Mayer, Celator Pharmaceuticals, Vancouver, BC	**Recent Scientific and Regulatory Developments in Preclinical and Clinical Bioanalytical Data Supporting GLP** Xiaowei Teng, BRI Biopharmaceutical Research Inc., Vancouver, BC
2:00-2:30	**Nanotechnology for Cancer Therapy; Lessons Learned from NCI's Nanotechnology Characterization Lab** Scott McNeil, SAIC-Frederick Inc./NCI at Frederick, Frederick, MD	**Health Canada and SCC Memorandum of Understanding – A Brief Overview of the Canadian GLP Program** Vesna Janic, GLP Inspector for SCC, Vancouver, BC
2:30-3:00	Poster Viewing and Break	
3:00-3:30	**Improving a Good Thing: Integrating Preclinical and Clinical Experience in the Development of Next Generation siRNA Products** Ian MacLachlan, Tekmira Pharmaceuticals Corporation, Burnaby, BC	**Challenges in Regulated Bioanalysis - A Case Study** Sanj Devarajan, ratiopharm, Mississauga, ON
3:30-4:00	**Regulatory and Scientific Approaches for Nanomedicines** Raimar Loebenberg, University of Alberta/Drug Development & Innovation Centre, Edmonton, AB	**Quality Management System for Bioanalysis Supporting Clinical Trials** Nageshwar Thudi, Ranbaxy Pharmaceuticals Canada Inc., Mississauga, ON
6:00 PM	**Pre-Gala Dinner Cocktails & Mixer** (Whistler Ballroom)	
7:00 PM	**CSPS GALA AWARDS DINNER** (Whistler Ballroom)	

Saturday, June 5, 2010	
8:30 AM	**Session VI** (Whistler Ballroom A)
	CHALLENGE ON HOW TO ALIGN PHARMACEUTICAL DEVELOPMENT WITH PAYOR AND CONSUMER NEEDS Chair: Brian Foster, Health Canada, Ottawa, ON
8:30-9:15	**The Need to Take on the Challenge of Alignment of Pharma with Payor Needs** Suzanne Taylor, BC Ministry of Health Services, Vancouver, BC
9:15-9:35	**Pharmacist Perspective** Marnie Mitchell, BC Pharmacist Association, Vancouver, BC
9:35-9:55	**Payor Perspective** Leza Muir, Blue Cross, Vancouver, BC
9:55-10:15	**Payor-Sponsor Scientific Dialogue** Mark Ferdinand, Rx&D, Ottawa, ON
10:15-10:35	**Through a Glass Darkly – The Future of Pharma** Mervyn Turner, Merck & Co. Inc., Merck Research Laboratories, Rahway, NJ
10:35	Panel Discussion - Open Forum
	Closing Remarks - Brian Foster
11:30 AM	Symposium Adjourned

AFPC Conference Program

First Annual Canadian Pharmacy Education and Research Conference (CPERC)

held jointly with the Canadian Society for Pharmaceutical Sciences (CSPS)

AFPC PROGRAM: Bringing the Blueprint to Life

DAY	ACTIVITY
Wednesday, June 2, 2010	
8:00 am – 5:00 pm	**AFPC, PEP Canada, CSPS and CCCP Business Meetings** – River Rock Casino Resort (RRCR) - Conference Centre (joint coffee breaks & lunch)
12 noon – 6:00 pm	**Exhibitor Set-up** (RRCR Theatre - Upper Floor Foyer)
3:30 pm – 7:00 pm	**Registration** (CPERC & CSPS Registration Desks - RRCR Theatre – Lower Floor Foyer)
5:30 pm – 7:00 pm	**Joint CPERC/CSPS Welcome Wine & Cheese Reception (**RRCR Theatre - Upper Floor Foyer - **Sponsored by Controlled Release Society)**
7:00 pm - 10:00 pm	**CPERC Opening Dinner & Awards Presentations by Faculty Award Winners** (RRCR Conference Centre - Fraser Room)
Thursday, June 3, 2010	
7:30 am – 5:00 pm	**Registration** (CPERC & CSPS Registration Desks - RRCR Theatre – Lower Floor Foyer)
7:30 am – 5:00 pm	**Exhibitors** (RRCR Theatre - Upper Floor Foyer)
7:30 am – 8:30 am	**Joint CPERC/CSPS Continental Breakfast** (RRCR Theatre - Upper Floor Foyer in Exhibit Area)
8:00 am – 6:30 pm	**Joint CPERC/CSPS Poster Presentations** (RRCR Theatre - Upper & Lower Floor Foyers)
8:30 am – 9:30 am	**Joint CPERC/CSPS Plenary Session (**RRCR Whistler Ballrooms A&B – **Sponsored by FMC Biopolymer)** **Keynote Speaker:** Dr. Pieter Cullis, University of British Columbia/CDRD, Vancouver, BC **"Lipid-Based Nanomedicines: Applications to Conventional Drugs and Genetic Drugs"**
9:30 am - 10:00am	**BREAK and Poster Viewing** (RRCR Theatre - Upper & Lower Floor Foyers; CPERC Delegates Move to RRCR Conference Centre – Fraser Room/CSPS Delegates Continue Program in RRCR Whistler Ballrooms)
10:00 am -12:00 pm	**CPERC Opening Session – "Framework for the Future – Critical Perspectives on Pharmacy Education & Practice"** (RRCR Conference Centre - Fraser Room) **Chair:** Simon Albon, BSc, MSc, Senior Instructor, UBC Faculty of Pharmaceutical Sciences **Speakers:**

	- **Robert A. Blouin**, PharmD, Professor and Dean, UNC Eshelman School of Pharmacy **"Patient Centered Care: Educating the Next Generation of Pharmacists"** - **Patricia (Paddy) Rodney**, RN, MSN, PhD, UBC School of Nursing **"Carrying the Blueprint Forward: Promoting Caring and Social Responsibility"**
12:00 pm – 2:00 pm	**AFPC Annual General Meeting & Luncheon** (RRCR Conference Centre - Thompson Room)
12:30 pm – 2:00 pm	**AFPC/CSPS First Annual Graduate Student Trainee Luncheon Session – "Pathfinding in the Pharmaceutical Sciences – Challenges & Rewards of an Academic Career"** (RRCR Conference Centre – Capilano & Birkenhead Rooms) **Chair:** Sam Gilchrist, PhD Candidate, UBC Faculty of Pharmaceutical Sciences, Linda Tran, PhD, UBC Faculty of Pharmaceutical Sciences **Speakers:** TBA
2:00 pm – 5:00 pm	**CPERC Workshop – "Bringing the Blueprint to Life in Pharmacy Education"** (RRCR Conference Centre – Fraser Room) **Afternoon Working Break** (3:00 – 3:30 pm in the RRCR Theatre - Upper Floor Foyer in Exhibit Area) **Chair:** Marion Pearson, BSc(Pharm), MEd, Senior Instructor, UBC Faculty of Pharmaceutical Sciences **Workshop Facilitator:** Barbara Gobis Ogle, BSc(Pharm), ACPR, MScPhm
5:00 pm – 6:00 pm	**Joint AFPC/CSPS Reception and Poster Viewing** (RRCR Theatre - Upper & Lower Floor Foyers - **Sponsored by Merck Frosst Ltd.**)
Free Evening	**An Opportunity to Enjoy Vancouver! Jump on the Skytrain!**
Friday, June 4, 2010	
7:00 am – 8:20 am	**Joint CSPS/AFPC Graduate Student Trainee Breakfast Session – Career Mentoring** (RRCR - Chairman's Room)
8:00 am – 4:00 pm	**Registration** (CPERC & CSPS Registration Desks - RRCR Theatre – Lower Floor Foyer)
8:00 am – 4:00 pm	**Exhibitors** (RRCR Theatre - Upper Floor Foyer)
8:00 am – 4:00 pm	**Joint CPERC/CSPS Poster Presentations** (RRCR Theatre - Upper & Lower Floor Foyers)
8:00 am – 8:20 am	**Joint CPERC/CSPS Continental Breakfast** (RRCR Theatre - Upper Floor Foyer in Exhibit Area)
8:30 am – 10:00 am	**CPERC Opening Session – "Supporting Intra-Professional Education & Experiential Learning – Perspectives from CPTEA and PEPC"** (RRCR Conference Centre – Fraser Room) **Chair:** Lynda Eccott, BSc, MSc, Senior Instructor, UBC Faculty of Pharmaceutical Sciences **Speaker from the Canadian Pharmacy Technicians Educators Association (CPTEA):** - Beverley Stotz, BSc(Pharm), RPh, Nova Scotia Community College **"Pharmacy and Pharmacy Technician Students Working Together"**

	Speakers from Pharmacy Experiential Programs of Canada (PEP Canada): - Cheryl Cox, BSP, MBA, Experiential Education Coordinator, Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta - Adrienne J. Lindblad, BSP, BSc, ACPR, PharmD, Clinical Practice Leader, Alberta Health Services **"Five Students: One Preceptor – Collaboration to Support Experiential Education"**
10:00 am - 10:30am	**BREAK and Poster Viewing** (RRCR Theatre - Upper Floor Foyer with Exhibits)
10:30 am – 12 noon	**CPERC Breakout Sessions – "Blueprint Pedagogies : Educating Medication Experts for a Changing Profession"** (RRCR Conference Centre – 4 Concurrent Sessions) **Breakout Session 1: "Faculty Recruitment: Preparing for the Blueprint and Ensuring the Right Knowledge, Skills, and Values Mix"** (Room: TBA) - **Mary H.H. Ensom**, Pharm.D., FASHP, FCCP, FCSHP, FCAHS, Professor and Director, Doctor of Pharmacy Program, UBC Faculty of Pharmaceutical Sciences - **Simon P. Albon**, BSc, MSc, Senior Instructor, UBC Faculty of Pharmaceutical Science **- James P. Kehrer**, Ph.D., Professor and Dean, University of Alberta, Faculty of Pharmacy and Pharmaceutical Sciences **Breakout Session 2: "Identifying and Mapping Pharmacy-related Interprofessional Learning Activities onto a Curriculum Framework using a World Café Discourse"** (Room: TBA) **- Lynda Eccott,** BSc, MSc, Senior Instructor, UBC Faculty of Pharmaceutical Science, Director of Interprofessional Curriculum, UBC College of Health Disciplines **- Donna Drynan,** M.Ed., OT(C), Clinical Associate Professor & Academic Fieldwork Coordinator, UBC Department of Occupational Sciences and Occupational Therapy, Director of Practice Education, UBC College of Health Disciplines - **Lesley Bainbridge,** BRS (PT), MEd, PhD, Associate Principal of the College of Health Discipline, Director of Interprofessional Education in the Faculty of Medicine - **Victoria Wood,** MA, Project Coordinator, UBC College of Health Disciplines. **Breakout Session 3: "Enhancing Learning and Assessment in Pharmacy Programs through Peer Teaching"** (Room:TBA) - **Marion Pearson**, BSc(Pharm), MA, RPh, Senior Instructor, UBC Faculty of Pharmaceutical Sciences - **Colleen Brady**, BSc(Pharm), RPh, Lecturer, UBC Faculty of Pharmaceutical Sciences - **Tessa Nicholl**, BSc(Pharm), MSc, RPh, Lecturer, UBC Faculty of Pharmaceutical Sciences **Breakout Session 4: "Developing a Program Evaluation for Canadian Faculties of Pharmacy"** (Room: TBA) - **Ingrid Price,** PhD, Senior Instructor, UBC Faculty of Pharmaceutical Sciences

12:00 pm – 1:30 pm	**Box Lunch: CPERC/CSPS Poster Viewing and Judging** (RRCR Theatre - Upper & Lower Floor Foyers)
1:30 pm – 2:00 pm	**AFPC Student Award Winner Presentations** (RRCR Conference Centre – Fraser Room) **Chair:** Mary MacCara, BSc(Pharm), ACPR, PharmD, Chair, AFPC Awards Committee **Award:** Canadian Foundation for Pharmacy-AFPC Graduate Student Award for Pharmacy Practice Research **Student Winner & Speaker: Ani Byrne,** BAS (Hons), MSc, University of Toronto, Leslie Dan Faculty of Pharmacy Award: **GlaxoSmithKline-AFPC Graduate Student Research Award** **Student Winner & Speaker: Melissa Carmen Cheung**, BSc, PhD Candidate, University of Toronto, Leslie Dan Faculty of Pharmacy
2:00 pm – 5:00 pm	**CPERC Research Symposium – "Foundations for the Future – Shaping Practice through Research"** (RRCR Conference Centre – Fraser Room) **Afternoon Break** (3:00 – 3:30 pm in the RRCR Theatre - Upper Floor Foyer in Exhibit Area) **Chair:** David Fielding, EdD, Professor and Associate Dean of Academic Programs, UBC Faculty of Pharmaceutical Sciences **Speakers:** **- Ross T. Tsuyuki**, BSc(Pharm), PharmD, MSc, FCSHP, FACC, University of Alberta **"The Blueprint is Nice, But Are Pharmacists Ready For It?"** - **Kelly Grindrod**, BScPharm, ACPR, PharmD, MSc, University of BC **Title:** TBA - **Carlo Marra**, BSc(Pharm), PharmD, Ph.D., FCSHP, University of BC **"Adaptation in B.C. – How did pharmacists do and did physicians like it?"** - **Suzanne C. Malfair Taylor**, BSc(Pharm), ACPR, PharmD, BCPS, FCSHP, Executive Director, Drug Use Optimization Branch, BC Ministry of Health Services **"Government perspective on pharmacy practice: the scoop on scope"**
5:30 pm	**Bus leaves RRCR for Downtown Vancouver & Dinner Cruise**
6:00 pm – 9:30 pm	**Dinner Cruise and CPERC-AFPC Awards Banquet** – cruising Coal Harbour, Stanley Park and False Creek (transport back to RRCR by Skytrain)
Saturday, June 5, 2010	
9:00 am – 12:00 pm	**CSPS Closing Session –** (Whistler Ballrooms A & B)
9:00 am – 12:00 pm	**AFPC New Council Meeting –** (Conference Centre – Lilooet Room)

Contents

CSPS POSTER PRESENTATIONS DAY 1

THURSDAY, JUNE 3, 2010

Speaker Abstracts

Plenary Session

(SPONSORED BY FMC BIOPOLYMER)

Lipid-Based Nanomedicines: Applications to Conventional Drugs and Genetic Drugs

Pieter Cullis, Department of Biochemistry and Molecular Biology, University of B.C.

Lipid-based nanoparticles (LNP) are by far the most advanced delivery systems for the systemic (intravenous) delivery of biologically active agents, with over seven clinically approved products and many others in advanced clinical trials. Two major areas of activity involve LNP delivery of small molecule "conventional" drugs and delivery of "genetic" drugs such as plasmid DNA and siRNA oligonucleotides. Advances in these areas will be reviewed and shown to support three general conclusions. First, the application of LNP technology to conventional drugs, such as anticancer drugs, can give rise to dramatic improvements in therapeutic index by improving efficacy and reducing toxicity of the encapsulated drug. Second, LNP delivery of genetic drugs such as plasmids can result in preferential delivery to disease sites such as tumour sites and tumour-specific gene expression. Finally, increasingly sophisticated LNP systems for i.v. delivery of siRNA oligonucleotides are resulting in remarkably potent systems for silencing target genes in vivo, particularly in the liver. Lipid-based nanomedicines that enhance the properties of conventional drugs and that enable macromolecules such as siRNA to be used as therapeutics will have an increasingly important clinical role.

Session I a

Prodrugs as Novel Therapies

PEG-based Prodrugs Improve the Anticancer Activity of Small Molecule Cytotoxics

Hong Zhao, Enzon Pharmaceuticals, Inc., Piscataway, New Jersey, USA

PEGylation is well known to decrease immunogenicity of protein and peptide and prolong circulating half-life. PEGylation has successfully produced several major marketed products. However, PEGylation of small molecules remains an emerging technology. By using innovative Customized Releasable PEG linkers, we show that PEGylation of small molecules can significantly increase solubility, provide extended exposure of the released cytotoxic, reduce unwanted toxicities, improve tumor accumulation of the cytotoxic agent, and most importantly, dramatically enhance antitumor activity in animal models. This methodology has been applied to improve the therapeutic index of several cytotoxic agents including SN38.

The utility of releasable PEG-cytotoxic will be demonstrated using a series of novel PEG conjugates, which were successfully synthesized with different Customized PEG Linkers for each small molecule drug. In general, while these PEG conjugates were stable in PBS buffer, they demonstrated a broad range of half-lives for release of the parent compound in rat and human plasma, varying from minutes to days. PEG conjugates with longer half-lives have shown prolonged circulation time and increased AUC of the released small molecule compared to native drugs in the PK studies in mice. In addition, PEGylation also greatly increased the water solubility for those insoluble molecules, for instance by about 1000-fold for SN38. In cellular based studies, PEG conjugates of cytotoxic molecules showed different degrees of anticancer activities against a panel of human cancer cells, which usually correlated with their plasma stability. Remarkably, enhanced anticancer activities compared to the non-PEGylated agent have been observed for many of the conjugates in a variety of cancer *in vivo* xenograft models, including both solid tumors and hematological malignancies. Customized PEG Linkers have demonstrated the ability to cause passive accumulation of drug molecules in tumors due to the enhanced permeation and retention (EPR) effect. All of these attributes contribute to the greatly enhanced anticancer efficacy of these PEG conjugates in animal models. In summary, Customized PEGylation applied to cytotoxic agents is a promising technology to improve therapeutic activity of current cytotoxic agents. One agent, PEG-SN38 is undergoing clinical evaluation in patients with advanced colorectal, breast, or pediatric cancers.

Role of Prodrug Design in Lead Optimization Strategy

Reza Oliyai, Senior Gilead Sciences, Foster City, CA, USA

The role of prodrug design to overcome biopharmaceutical challenges resulting from low permeability, poor aqueous solubility, and inadequate drug targeting to particular diseased tissues during lead optimization will be discussed. A series of case studies as examples of successful prodrug approaches will be presented.

Development of a Weak-Base Docetaxel Derivative that can be Loaded into Liposomal Nanoparticles

Norbert Maurer, Centre for Drug Research and Development (CDRD), Vancouver, BC, Canada

Hydrophobic uncharged drugs such as docetaxel are difficult to encapsulate and retain in liposomal nanoparticles (LNP). We have shown that a weak base derivative of docetaxel can be actively loaded into LNP using pH gradient loading techniques to achieve stable drug encapsulation and controlled

release properties. Docetaxel was derivatized at the hydroxyl group in the C-2' position to form an N-methyl-piperazinyl butanoic acid ester. The free hydroxyl group in this position is essential for anticancer activity and the prodrug has, therefore, to be converted into the parent drug (docetaxel) to restore activity. Cytotoxicity testing against a panel of cancer cell lines (breast, prostate and ovarian cancer) demonstrated that the prodrug is readily converted into active drug; the derivative was found to be as active as the parent drug in vitro. The docetaxel derivative can be efficiently loaded at high drug-to-lipid ratios (up to 0.4 mg/mg) into LNP using pH loading techniques. Pharmacokinetic, tolerability and efficacy studies in mice demonstrate that the LNP-encapsulated prodrug has the long drug circulation half-life required for efficient tumor accumulation (50-100 times higher drug plasma levels compared with free derivative and Taxotere™, the commercial docetaxel formulation), is active in a xenograft model of breast cancer (MDA-MB-435), and is well tolerated at i.v. doses of 3 times higher than the maximum tolerated dose of the parent drug. This is the first demonstration that a therapeutically active, remote-loaded, controlled-release LNP formulation of a taxane can be achieved. The approach reported here has broad applicability to other approved drugs as well as new chemical entities.

Novel Bone-targeting Prostaglandin EP4 Receptor Agonist-bisphosphonate Pro-drug Conjugates as Dual Action Therapies for Treatment and Reversal of the Effects of Osteoporosis

Robert Norman Young, Stephen Arns, Monzur Morshad, Anne Moreau, Department of Chemistry, Simon Fraser University, Burnaby, BC, Canada.

Many safe and effective drugs exist (e.g. bisphosphonates such as alendronate) that inhibit the excessive bone resorption associated with osteoporosis. Unfortunately there are few useful drugs available that can induce bone growth and thus act to restore bone lost in this disease. Prostaglandin E2 (PGE2) is known to stimulate bone growth in animals and in humans. Unfortunately PGE2 exerts many effects in the body, including unacceptable gasterointestinal (G.I.) side effects, and PGE2 has been shown to mitigate these effects through interactions with at least four receptor subtypes (termed EP1, EP2, EP3 and EP4). Studies demontrate that PGE2 induces bone growth through activation of the EP4 receptor subtype and several EP4 selective agonists have been identified. Unfortunately these compounds also induce G.I. side effects in animals thus limiting their use. Bisphosphonates target bone and form essentially irreversible complexes with apatite in vivo and co-administration of alendronate with PGE2 has been shown to be additive for effect on bones. Thus we have designed a number of conjugates of known, potent, EP4 selective agonists with alendronate. These novel dual pro-drug conjugates are joined by linker functions that, on enzymatic hydrolysis, liberate both the free
alendronate and the free agonist over extended periods of time. In order to observe and quantitate the uptake into bone and slow liberation of the active components we have synthesized the conjugates in radio-labelled form. The design and synthesis of these conjugates and their in vitro and in vivo properties in rats will be described. Such conjugates may represent novel, dual action therapy for treatment and reversal of the effects of osteoporosis.

Session I b

New Advances in Drug Metabolism and Disposition: Genetic Versus Environmental Influences

Altered Drug Metabolism and Transport in Cancer and Cachexia

Arran Painter[1], Lucy Jankova[1], Joel Chick[2], Maria Tsoli[1], Marina Kacevska[1,3], Mark Baker[2], Chris Liddle[3], Mark Molloy[2], Stephen Clarke[1], **Graham Robertson[1]**, [1]Cancer Pharmacology Unit, ANZAC Research Institute, Concord Hospital, Sydney, AUSTRALIA; [2]Australian Proteome Analysis Facility, Macquarie University, NSW Australia; [3]Storr Liver Unit, Westmead Millennium Institute, Australia.

A major challenge in pharmacogenomics is the narrow therapeutic index of anti-cancer treatments, as toxicity due to variable drug clearance is a common cause of treatment failure. It appears that systemic inflammatory repsonses associated with tumours is responsible for repression of hepatic drug clearance - in particular CYP3A4. Elevated inflammatory markers coupled with tumour-derived cytokines such as IL-6 are also significant features of the metabolic imbalance underlying tissue wasting in cachectic cancer patients. Therefore disrupted drug clearance and aberrant regulation of metabolic pathways may be part of the same process and in combination impact on treatment outcome and quality of life for many cancer sufferers.
We have made use of mouse tumour models of cachexia to characterize the alterations in drug metabolizing enzymes & transporters as well as to explore the interplay of cytokine signaling with nuclear receptors and other key regulators of drug clearance and general lipid and carbohydrate metabolic pathways.

Transcriptional repression of a human *CYP3A4* transgene in tumour-bearing mice was accompanied by increased IL-6, activation of downstream components of the IL-6 signalling cascade (Phospho-STAT3, MAPKs, SOCS3 mRNA) and increased expression of hepatic acute phase proteins. Extensive expression profiling by cDNA microarrays and MS-based proteomic profiling showed that all 3 phases of hepatic drug metabolism and transport are altered in tumour-bearing mice. The underlying mechanism may involve disrupted action of RXRą the heterodimeric partner of many nuclear receptors that regulate drug clearance and other metabolic pathways. Pharmacokinetic and biodistribution studies exploring the functional outcome of these changes in drug metabolising & transport proteins as well as interventions aimed at normalizing drug clearance in tumour-bearing mice as a prelude to clinical trials will also be described.

Pharmacogenomics of Drug Disposition: Theory and Application

Anahita Bhathena, Pharmacogenetics, Abbott Labs, Abbott Park, Illinois, USA

Multiple drug metabolizing enzymes and drug transport proteins contribute to drug disposition. Genetic polymorphisms within the genes for these proteins can result in inter-individual variability in drug pharmacokinetics. Increased understanding of the genetic basis for pharmacokinetic variability leads to improvements in therapeutic treatment decisions and the safer use of drugs.

Genetic polymorphisms within drug disposition pathways are well characterized – while the Cytochrome P450s have been the most extensively studied, substantial information has been generated in recent years for other drug metabolizing enzymes (for example, sulfotransferases and glucuronosyl-transferases) and the drug transport proteins. The availability of both, scientific information and the technical tools for assessing genetic variability in drug disposition pathways has resulted in significant progress in the field.

Pharmacogenetic information is included in several drug labels and may be used to improve clinical treatment decisions. Recently, for example, the drug labels for warfarin and clopidogrel were updated to include pharmacogenetic information on drug disposition.

During drug development ADME pharmacogenetic studies are routinely conducted to

explore inter-individual pharmacokinetic variability, and may contribute information for dose escalation decisions, planning drug-drug interaction studies, and to understand the potential consequences of the pharmacokinetic variability for efficacy, safety, and development of the new molecular entity.

Genetic and Environmental Regulation of Drug Metabolizing Enzymes and Transporters by Nuclear Receptors

Wen Xie, Center for Pharmacogenetics and Department of Pharmaceutical Sciences, University of Pittsburgh School of Pharmacy, Pittsburgh, PA

Abstract: We study nuclear receptor-mediated regulation of genes encoding drug metabolizing enzymes and transporters. The same enzyme and transporter systems are also responsible for the detoxification and homeostasis of numerous endogenous substances, including bile acids and sex hormones. As such, the nuclear receptor-mediated gene regulatory network has broad implications not only in drug metabolism, but also in establishing nuclear receptors as therapeutic targets for human diseases. We are interested in the roles of pregnane X receptor (PXR), constitutive androstane receptor (CAR), liver X receptor (LXR) and retinoid-related orphan receptor (ROR) in the regulation of drug metabolizing enzymes and transporters. To better understand the *in vivo* function of these receptors, we have created a wide array of genetically engineered mice that include transgenic, knockout and "humanized" mice. Various disease models are incorporated into the animal models. This presentation will focus on the role of LXR in regulating hormone metabolizing enzymes, and the implications of this regulation in drug-hormone interaction and hormone-dependent breast cancer and prostate cancer. The endobiotic functions of several "xenobiotic receptors," such as CAR and AhR, will also be discussed.

Regulation of Drug Transporters and its Impact on Drug Response and Kinetics

Micheline Piquette-Miller, Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, ON

Drug transporters which play a critical role in the absorption, distribution and clearance for numerous drugs, toxins and their metabolic products are increasingly being recognized as key determinants of drug response. Several efflux and influx transporters that are highly expressed in biologically protective barriers of the liver, intestine, kidney, blood brain barrier and placenta, profoundly impact the passage of xenobiotics across these membranes. Thus changes or defects in transporter function can significantly contribute to altered efficacy and toxicity. Findings over the past 5-10 years have attributed a number of environmental, pathophysiological and genetic factors as sources of variability. In addition to genetic polymorphisms, significant inflammation-mediated changes in the expression of many of the ABC drug efflux transporters and organic anion drug uptake transporters have been demonstrated to impact drug distribution and clearance. Moreover regulation by nuclear hormone receptors such as the pregnane X and constitutive androstane receptors have been identified as important sources of environmental control. These advances have contributed greatly towards understanding the regulation of transporters and their role in variable drug response.

Session II a

New Directions in Clinical Applications of Delivery Systems for Cancer Treatment and Diagnosis

(SPONSORED BY BAYER)

Opportunities for Combination Medical Devices in Local siRNA Delivery and Therapeutics

David W. Grainger, Department of Pharmaceutics and Pharmaceutical Chemistry, University of Utah, Salt Lake City, UT, USA

Combination devices are approved medical prosthetic implants augmented with on-board drug release or delivery capabilities to enhance their primary mode of performance (Wu and Grainger, Biomaterials, 2006). After surgical placement, these implanted devices release drug locally to the implant-tissue interface for specific purposes that enhance implant safety and efficacy. On-board drugs can mitigate infections or thrombosis, reduce inflammatory responses, and promote tissue regeneration. Drugs with difficult systemic delivery requirements or low therapeutic indices, including protein, cell and nucleic acid therapeutics, can be more readily delivered locally from implants where appropriate. We have used this approach recently to deliver siRNA therapeutics that also exhibit problematic systemic targeting issues. Specifically, we have sought to control osteoclast-mediated excessive bone resorption central to several systemic and local bone loss pathologies, including osteoporosis. We demonstrate the potential for siRNA control of osteoclast function using siRNA against RANK to suppress osteoclast formation and its intrinsic bone resorption activities. Delivery of siRNA targeting RANK to both RAW264.7 and primary bone marrow cell cultures produces short-term RANK suppression without off-targeting effects, and significantly inhibits both osteoclast formation as determined by tartrate-resistant acid phosphatase (TRAP) assay, and subsequent bone resorption by resorption pit assay. Successful RANK knock-down by siRNA specifically in mature osteoclast cultures in serum-containing media has allowed us to move in vivo using siRNA formulations in bone augmentation materials. (Wang and Grainger, Pharm. Res., 2010) Another study is focused on delivering siRNA targeting FRAP1 (also mTOR), a serine/threonine kinase controlling cell proliferation and mobility, from implants. (Takahashi et al., submitted, 2010) Since fibrous encapsulation of surgically implant devices is associated with elevated proliferation and activation of fibroblasts in tissues surrounding these implants, frequently causing foreign body complications, we test the hypothesis that inhibition of mTOR expression in fibroblasts can mitigate soft tissue implant foreign body responses by suppressing fibrotic responses around implants. siRNA targeting mTOR was delivered with branched cationic polyethylenimine (bPEI) to fibroblastic lineage cells in serum-based cell culture as shown by both gene and protein analysis. This mTOR knockdown inhibited fibroblast proliferation by 70% with simultaneous down-regulation in the expression of type I collagen in fibroblasts *in vitro*. These siRNA/bPEI complexes were then released from poly(ethylene glycol)-based hydrogel coatings on model polymer implants in a subcutaneous rodent model. No significant reduction in fibrous capsule thickness and mTOR expression in the foreign body capsules was observed. siRNA inefficacy in this implant model was attributed to siRNA dosing limitations in the gel delivery system, and lack of targeting ability of the siRNA complex specifically to fibroblasts. While in vitro data supported mTOR knock-down in fibroblast cultures, in vivo siRNA delivery must be further improved to produce clinically relevant effects on fibrotic encapsulation around implants.

Polymeric Micelles for Combinatorial Drug Delivery

Glen S. Kwon, School of Pharmacy, University of Wisconsin, Madison, WI, USA

Polymeric micelles have attracted a lot attention in drug delivery due to proven safety and rapid progress in drug solubilization, especially in the cancer area. Poly(ethylene glycol)-block-poly(lactic acid) (PEG-b-PLA) micelles have entered phase II clinical trials in the USA and have gained approval in Korea as a vehicle for paclitaxel (Genexol-PM®), offering a safer vehicle for this poorly water-soluble cancer drug over Cremophor EL (Taxol®). Cremophor EL causes severe toxicities, including acute hypersensitivity reactions despite premedication. The maximum tolerated dose (MTD) of Genexol-PM® in a phase I clinical trial was 300 mg/m2, whereas the MTD for Taxol® is 135 to 200 mg/m2. In this work, we show that PEG-b-PLA micelles can take up and solubilize multiple cancer drugs: paclitaxel, 17-allylamino-17-desmethoxygeldanamycin (17-AAG) and rapamycin in aqueous solution. 17-AAG inhibits heat shock protein 90 (Hsp90), which acts as a chaperone for "client proteins," many of which are involved in cancer-causing and survival pathways. Rapamycin inhibits mTOR, a serine-threonine kinase, which plays a central role in cell growth, proliferation, survival and angiogenesis. Two-drug combinations of paclitaxel + 17-AAG and paclitaxel + a slightly water soluble analogue of rapamycin (CCI-779) are in clinical trials, but with Cremophor EL, DMSO/lipid and/or ethanol as vehicles for drug solubilization. PEG-b-PLA micelles offer a simple, safe, soluble and sterile option for a 3-drug combination of paclitaxel, 17-AAG and rapamycin for multiple drug delivery, aiming for synergy in cancer therapy.

Nanotechnology Applications in Cancer Diagnosis and Therapy

Mansoor M. Amiji, Department of Pharmaceutical Sciences, Nanomedicine Education and Research Consortium (NERC), Northeastern University, Boston, MA, USA

There has been tremendous recent interest in nanotechnology application for disease prevention, diagnosis, and treatment. For many diseases, such as cancer, early diagnosis and overcoming biological barriers and target specific delivery are the key challenges. Additionally, newer generation of molecular therapies, such as gene therapy oligonucleotides, and RNA interference, require robust and highly specific intracellular delivery strategies for effective therapeutic outcomes.

In this presentation, I will provide an overview of our work over few years in nanotechnology for target specific delivery of drugs and genes. We have developed metal, polymer, and lipid-based nano-platforms for diagnosis and delivery of therapeutics and image contrast agents. Peptide-modified gold nanostructures were developed for early cancer detection. Using biodegradable polymers, we have formulated nanocarriers for systemic delivery of hydrophobic anticancer drugs and therapeutic genes. Additionally, we have developed nanoemulsions, using oils rich in omega-3 polyunsaturated fatty acids, which can facilitate drug delivery across different biological barriers, such as the blood-brain barrier.

Targeted Nano-Therapeutics for the Treatment of Resistant Cancers

Afsaneh Lavasanifar, Faculty of Pharmacy & Pharmaceutical Sciences, University of Alberta, Edmonton, AB; Canada

Cancer is set to supplant cardiovascular disease and become the number one cause of death in north America. Despite significant strides in understanding the mechanisms behind cancer, efficient and curative therapies are still missing. Chemotherapy is the treatment of choice in many cancers. However, it rarely cures cancer and mostly becomes ineffective by drug resistance. Moreover, emergence of intolerable toxicities by chemotherapeutic agents lowers the quality of life significantly, in cancer patients. Immunotherapy is the more recent and unconventional form therapy for cancer, which is also not curative. Recent research has provided a strong case for the potential benefit of combined immuno and chemotherapy in the eradication of cancer. In both cases achieving high therapeutic efficacy requires targeted delivery –to cancer cells and its microenvironment in case of chemotherapy and to antigen presenting cells in case of cancer vaccines.

The objective of our research is to design targeted vaccine and drug delivery systems that can enhance the efficacy and reduce the toxicity of

immunotherapy and chemotherapy in cancer. The long-term goal of this research is synergistic combination of immunotherapy with chemotherapy, taking advantage of the capabilities of targeted delivery systems for each approach. In this presentation a brief update on the progress made by our research group in the design and development of nano-therapeutics for targeted anticancer drug delivery to cancer cells and enhanced vaccine delivery to dendritic cells (DCs) will be provided. In this context, development of engineered poly(ethylene-oxide)-*b*-poly(ε-caprolactone) (PEO-*b*-PCL) based block-copolymer micelles containing cancer-specific peptide ligands on their surface as targeted nano-therapeutics that can enhance efficacy and reduce toxicity of chemotherapeutics in sensitive and resistant cancer phenotypes will be described. An overview on the development of poly (D,L-lactic-*co*-glycolic acid) (PLGA) nanoparticles surface grafted with ligands for DCs as targeted cancer vaccine delivery systems with the objective of enhanced T cell mediated immune responses capable of mediating rejection of established tumors in animal models, will be provided.

Session II b

Biomarkers (For Preclinical Development, Toxicology, Clinical Trials)

What Pharma Needs with Respect to Biomarkers – COPD as an Example

Bruce E. Miller, Discovery Medicine, Respiratory Centre of Excellence for Drug Discovery, GlaxoSmithKline, King of Prussia, PA, USA

Many common chronic diseases such as diabetes, osteoporosis, rheumatoid arthritis, asthma and chronic obstructive pulmonary disease (COPD) are continuing to increase in prevalence and have substantial unmet medical need. Drug development for many of these diseases has been challenging because many of the clinical endpoints needed to support regulatory approval require studies of long duration and large numbers of subjects. Compounding this situation is the fact that in recent years many late stage trials have failed to demonstrate efficacy making the investment decisions in new therapies uncertain. To avoid some of these obstacles and allow for better decision making during a clinical trial program, new approaches are needed. Biomarkers can be useful tools for facilitating drug development by helping to identify patient subgroups most likely to derive clinical benefit, facilitate dose selection to maximize efficacy and understand or mitigate safety risks, obtain intermediate measures of pharmacology and better understand the underlying basis for disease progression. The proper use of biomarkers may help to remove some of the uncertainty inherent to the current development processes, thus allowing for more informed decision making at each stage of drug development. In recent years, several regulatory authorities have established or are in the process of implementing guidelines for the submission, review and approval of biomarkers. This has lead to focused efforts to gain acceptance of a number of biomarkers for specific uses and indeed the US FDA and other regulatory agencies have approved a number of biomarkers for certain uses. Our group is evaluating several promising biomarkers that are likely to have utility in supporting novel drug development in COPD. Data to support biomarker use may come from a variety of sources, including the scientific and medical literature and observational and interventional studies. Careful attention must also be given to the methodology used to obtain the biomarker data to ensure that it is sufficiently robust and appropriately validated. Several examples will be discussed to illustrate the type of information that is needed to

support biomarker development and acceptance to help facilitate drug development.

What the Diagnostic Industry Can Offer

Mike Pintek, Luminex Corporation, Austin, TX

1. The diagnostics industry today:
(a) Growing aging population; (b) Increasing cost-containment issues; (c) Single tests.
2. View of the current science:
(a) Projection of where the science is going and what answers it will provide; (b) Clinical benefits; (c) Social considerations.
3. Multiplexing as a powerful tool for diagnostics:
(a) Benefits of multiplexing; (i) Single sample, single run, same instrument, multiple answers; (ii) Nucleic acids and protein on same platform; (iii) Identify co-infections; (iv) Addition of new assays, scale up.
4. Benefits of new technologies in the diagnostics market:
(a) Lab-on-a-Chip; (b) Next Gen Sequencing; (c) Personalized Medicine; (d) Biomarkers.
5. Examples of Luminex xTAG® technology in action:
(a) RVP; (b) Cancer (glioblastoma); (c) Cystic Fibrosis; (d) Predictive drug therapy (2D6, 2C19).
6. A robust pipeline for the future:
(a) MAGPIX; (b) NBS; (c) GI, fungal, CNS panels.

Biomarkers in Transplantation (BiT): From Purpose to Discovery and Validation of Signatures of Immune Rejection

Bruce McManus for the BiT Team and the NCE CECR Centre of Excellence for Prevention of Organ Failure (PROOF Centre), Vancouver, British Columbia

Purpose: Immune rejection of transplanted allografts such as hearts and kidneys constitutes as significant threat to the survival of the precious organ, and indeed, of the recipient patient. The detection of rejection is typically accomplished by use of invasive tissue biopsies that are costly, potentially risky, fear-evoking and uncomfortable for patients, and subjectively interpreted.
Approach and Results: The desire to improve the monitoring process for acute or chronic rejection in heart and kidney allograft recipients has prompted the BiT Team and the PROOF Centre of Excellence to discover and begin validating genomic and proteomic biomarker classifier panels derived from PAXgene whole blood Affymetrix-based transcriptome profiling and depleted plasma iTRAQ-MALDI-TOF/TOF analysis that discriminate rejectors and non-rejectors, either diagnostically or predictively. The classifier panels have been compared to those derived by the FDA and others, and are in an advanced state of refinement. A multi-national validation trial is underway in which the biomarker classifier panels will be rigorously appraised for their practical utility and reliability.
Conclusion: The experience gained in the realm of transplant rejection has provided a framework for the evolving discovery programs and assay development programs of the PROOF Centre, now embracing and working on clinically daunting points in the life cycles of risk and disease that underpin heart, lung and kidney failure of native organs. The impact that the PROOF Centre hopes to have requires a cross-disciplinary team, many partners from all sectors, an international perspective, and a focused, yet flexible strategy. With competitive national funding and mutually-leveraged funding from like-minded partners, the PROOF Centre is moving forward to make molecular biomarker solutions a predictive, diagnostic and prognostic reality for those suffering from vital organ failure. The strategy includes the guidance of current pharmaceutical therapies and assistance in the development of new, more effective drugs.

Bringing the Community Together for Efficient Biomarker Strategies

Shawnmarie Mayrand-Chung, The Biomarkers Consortium, Bethesda, Maryland, USA

The genesis of the Biomarkers Consortium was initially with PhRMA, the trade organization for the pharmaceutical industry. In discussion with the NIH and FDA, the shared need for robust and meaningful biomarkers, well characterized for use and widely available to all, was self-evident. In light of the differing missions of the parties, the value of biomarkers to each also differs somewhat, but the need is compelling for each of the partners. Furthermore, the value proposition for working in the context of a public-private partnership provides additional motivation for each of the parties participating in the BC.
The value proposition for NIH lies within the agency's mission to improve the public health through biomedical research. The scope of the

research undertaken within the NIH's 27 institutes and centers ranges from basic mechanistic work, to elucidate underlying biological mechanisms of health and disease all the way, to late phase clinical trials, and includes everything between those two poles. Biomarkers are both indicators of biological mechanisms as well as serving as probes for pathobiological processes. To the extent that biomarkers may serve as a bridge connecting animal models of disease with human signs and symptoms of disease, they provide an excellent tool for translational research. Biomarkers in the setting of clinical research allow for the detailed characterization of patients, allow stratification of subjects in clinical trials, and can demonstrate evidence of the effect of study interventions. And finally, biomarkers will provide useful and novel tools for clinical decision-making.

The structure of the BC rests on the premise that all activities of the BC will be pre-competitive in nature. This translates to mean that the goal and expected outcome of BC activities is not to generate new intellectual property, but rather to generate new knowledge and information that will be made available to the public (There are a number of nuances to this statement relating to human subjects protections, the use and contribution of pre-existing IP to the activities undertaken within the BC, and possible regulatory applications that may relate to BC generated work products that will be discussed further below). Working together in pre-competitive projects will, the BC expects, generate information and knowledge that will be the basis for future commercial applications such as the development of tests and diagnostics that extend and apply the information and knowledge generated in the BC.

Sunrise Session

CSPS/AFPC Trainee Breakfast Session: Career Mentoring

The Career Mentoring Breakfast - Friday, June 4 from 7:00–8:20 AM. This breakfast will give graduate students and undergraduates an opportunity to openly discuss potential challenges related to future career transitions with professional mentors from academia, industry and government. Small-group roundtable discussions will focus on various topics.

Session III

Award Winner Presentations

CSPS Leadership Award Co-Winner

CanReg: The Successful Convergence of Government, Academia and Industry

Anne Tomalin, CanReg Inc., Dundas, ON

CanReg Inc, a regulatory consulting company formed in Hamilton, Ontario in 1996, is an example of the successful convergency of Government, Academia and Industry. All three areas helped form and develop this company as it became the No. 1 Regulatory Consulting Company in Canada, and possibly in the world. In December 2009, i3 Research, a large US-based company which is a part of United Health, acquired this thriving Canadian company. This decision will benefit the next step in the growth of this company and result in even more jobs for Canadians with skilled scientific training.

CSPS Leadership Award Co-Winner

Adventures of a Serial Entrepreneur

Pieter Cullis, University of British Columbia/CDRD, Vancouver, BC

I have been involved in starting up six biotechnology companies, including Lipex Biomembranes, The Canadian Liposome Company, Inex Pharmaceuticals (now Tekmira Pharmaceuticals), Northern Lipids Inc., Protiva Biotherapeutics and most recently AlCana Technologies Inc. In between I have played a major role in founding the Centre for Drug Research and Development, a BC-based initiative that is aimed at enhancing the probability that early stage academic discoveries in the life sciences lead to new therapeutics to treat human disease. These initiatives have led to two approved new drug products, five more drugs in clinical trials, over $200M of investment and over 1,000 man-years of employment in the biotechnology sector in BC. As will be explained, this was accomplished employing three simple maxims: don't be afraid to take a chance, build a team and keep it together and have a party whenever possible.

GlaxoSmithKline Early Career Award Winner

The Liver X Receptors in the Regulation of Cholesterol and Glucose Metabolism

Carolyn L. Cummins, University of Toronto, Toronto, ON, Canada

The liver X receptors (alpha and beta) are members of the nuclear hormone receptor family that are activated by endogenous cholesterol metabolites. These receptors are widely expressed with a tissue distribution that includes the liver, intestine and macrophage. Upon activation, these receptors have been shown to increase reverse cholesterol transport from the macrophage back to the liver to aid in the removal of excess cholesterol. Furthermore, they have also been shown to inhibit the inflammatory response in macrophages. These functions are accomplished through direct regulation of gene transcription. My recent data has demonstrated that LXR is also important for regulating glucocorticoid synthesis and cholesterol homeostasis in the adrenal gland in response to chronic dietary stress. These data suggest LXR provides a molecular link to glucocorticoid signaling which is the current focus of my laboratory. I will describe the key benefits and potential risks of targeting the LXRs for the treatment of atherosclerosis and metabolic disease.

Session IV a

siRNA as *In Vivo* Therapeutics

(SPONSORED BY MERCK)

Small Interfering RNA as a Therapeutic Modality

Alan Sachs, Merck Research Laboratories/ Sirna Therapeutics, San Francisco, CA

Small interfering RNA (siRNA) utilizing a common gene silencing pathway has become a widely used research tool to probe gene function. The therapeutic potential of siRNA is now becoming realized through treatment of diseased tissues by silencing specific gene targets. The broader feasibility for treating systemic disease is hindered by poor siRNA stability, limited tissue uptake, activation of the innate immune response, and off-target gene silencing. Overcoming many of these barriers is made possible through chemical modification of oligonucleotides. Chemical modification (>50%) protects siRNA from nuclease degradation, abrogates inflammation, and reduces off-target gene silencing thereby enhancing selectivity for the intended target. Delivery vehicles composed of lipid and other polymers allows for enhanced tissue uptake. Therapeutic siRNAs enabled in this manner can enhance drug development through diverse clinical applications for human target validation and interfering with disease pathways. Consequently, therapeutic siRNA can be harnessed to open a new frontier for drug development.

Progress in the Development Delivery Systems for siRNA

Mark A. Tracy, Alnylam Pharmaceuticals Inc., Cambridge, Massachusetts, USA

The development of approaches for delivering siRNA to desired cells *in vivo* is essential to realize the full potential of this class of molecules as therapeutics. Significant progress has been made over the last couple of years in advancing the science of siRNA delivery and in translating this knowledge to the clinic. As a result, multiple delivery approaches have now been used in the clinic for both local (or direct) and systemic delivery. This presentation will discuss the progress in developing multiple approaches with a focus on delivery of siRNA by lipid particles. Lipid nanoparticle delivery systems (LNPs) represent one of the few systemically administered delivery systems for siRNA that have entered the clinic. This presentation will provide a review of recent data supporting the advancement of a lipid particle formulation to the clinic and will discuss advances in research offering the potential for improved formulations in the near future. In particular, the discovery of new lipids has resulted in the improvement in potency of next generation formulations of up to 2 orders of magnitude for some liver targets. Also, improvements in the understanding of key formulation variables and mechanisms of cellular uptake of lipid nanoparticles (LNPs) may result in improved targeting and delivery to a greater variety of locations or cell types within the body. Progress in direct delivery of siRNA to, for example, the CNS will also be discussed. These results support the potential of RNAi therapeutics as a new class of pharmaceuticals for the treatment of a variety of diseases.

Membrane/Core Type Nanoparticles for Co-delivery of siRNA and Doxorubicin

Leaf Huang and Yun-Ching Chen, Eshelman School of Pharmacy, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

In the mid 90s, our group has developed two nanoparticle formulations for DNA delivery. Although the core was made of DNA/protamine complex, LPD-I contained a cationic lipid

membrane and LPD-II contained an anionic lipid membrane. In the last few years, we have modified both formulations for efficient intravenous delivery of siRNA to the tumor. The surface membrane was grafted with a thick PEG brush such that the nanoparticles were not taken up by the reticuloendothelial system (RES) and accumulated with high efficiency in the tumor by the enhanced permeability and retention effect. siRNA so delivered could effectively silence the target gene and brought about tumor growth inhibition. Furthermore, we have loaded the DNA with doxorubicin and used it to formulate siRNA in the same nanoparticle. Both LPD-I and LPD-II could co-deliver siRNA and doxorubicin to overcome P-gp mediated drug resistance in the tumor. Since LPD-II does not contain cationic lipid, its inflammatory toxicity was lower than that of LPD-I. Research supported by NIH grant CA129835.

Ionizable Cationic Lipids and In Vivo Delivery of siRNA: How Low Can we Go?

Michael Hope, AlCana Technologies, Vancouver, BC

Lipid nanoparticles (LNP), containing ionizable cationic lipids, are remarkably effective at intracellular delivery of siRNA into hepatocytes following intravenous administration to rodents and non-human primates, and first generation LNP-siRNA are currently undergoing clinical testing in multiple Phase I trials. Although these nucleic acid delivery systems have been in development for many years, it is only since being applied to siRNA that their potency has been fully realized. The cationic lipid component of LNP-siRNA delivery systems is critical to particle self assembly, stability, tolerability and in vivo activity. Guided by a well developed hypothesis concerning in vivo mechanism of action at the molecular level for LNP containing ionizable cationic lipids, we have applied a systematic, rational design approach to the discovery of new and more potent lipids to be used in the next generation siRNA delivery systems. A robust and well characterized model was used to screen for LNP activity in vivo. LNP encapsulating siRNA against murine FVII were made using each cationic lipid to be tested and FVII protein concentrations in serum were measured 24h following intravenous administration of the delivery system. By administering a range of siRNA doses the amount of siRNA capable of reducing serum FVII protein concentrations by 50% (ED_{50}) was determined for each cationic lipid tested. Several hundred cationic lipids have now been synthesized, formulated and screened for activity using this model, allowing us to identify critical molecular features. Lipids and formulations have been identified with ED_{50} doses of FVII siRNA as low as 10µg/kg (equivalent to 0.2µg siRNA per mouse). These dose levels are so low that it is interesting to speculate on how much more room for improvement there is for this class of siRNA delivery system, capable of such potent delivery of siRNA payloads into the cytoplasm of hepatocytes in vivo.

Session IV b

Role of Lipids in Modifying Oral and Parenteral Drug Delivery

Lipid Based Formulations of Anticancer Drugs: What's In and What's Out

Marcel Bally, Experimental Therapeutics (BC Cancer Agency); and Division of Pharmacology and Toxicology (Centre for Drug Research and Development), Vancouver, BC

[Abstract not available]

Lymphatic Transport of Drugs

Christopher J.H. Porter, Monash Institute of Pharmaceutical Sciences, Monash University, Parkville, Melbourne, Australia

The lymphatic system comprises a network of vessels, nodes and areas of aggregated lymphoid tissue distributed throughout the vascular regions of the body. The lymphatics are primarily responsible for the maintenance of fluid balance, but also play a significant role in the intestinal absorption and transport of neutral fats and in the maintenance of an effective immune defence mechanism. The unique anatomy and physiology of the lymphatics dictates that promotion of drug delivery to, or via, the lymphatic system may provide a number of pharmacokinetic and pharmacodynamic advantages. These include a reduction in first pass metabolism and targeted drug exposure to eg lymph resident metastases, viruses including HIV, and components of the immune system including lymph nodes and lymphocytes. Drug (or drug delivery system) access to the lymphatics can occur after both oral and parenteral administration, but in both cases is dictated largely by size, due to the higher permeability of the lymphatic vs vascular endothelium. Thus, macromolecular species injected subcutaneously preferentially drain into the capillaries of the lymphatics rather than the blood due to poor permeability across the vascular endothelium. After oral administration, lymphatic access is facilitated by drug association with colloidal lipoproteins in the enterocyte, the size of which precludes ready diffusion into the blood, but allows transport into the lymph. Lymphatic transport after oral administration is therefore dependent on drug lipophilicity to facilitate lipoprotein association. Historical predictions of the potential for lymphatic drug transport have centered on the use of simple physicochemical descriptors of lipophilicity such as lipid solubility and partition co-efficient, but recent data suggest that in certain cases this may be an oversimplification and that lymphatic transport may be driven by an affinity for lipoprotein components other than the non-polar lipid core. An interesting recent development is the potential for lymphatic transport to impact not only on drug pharmacokinetics, but also pharmacodynamics, particularly where activity at the level of enterocyte-based lipoprotein assembly is envisaged. In summary, the lymphatics provide an attractive alternative route of drug delivery for certain applications and an increasing level of understanding of the drivers of drug access provides increasing confidence in the potential for rationally promoting or maximizing lymphatic transport.

Role of Lipids and Lipoproteins in modifying the Pharmacokinetics and Tissue Distribution of Hydrophobic Drugs

Dion Brocks, Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, AB

Hyperlipidemia is a major risk factor for the development of serious cardiovascular diseases such as myocardial infarction and stroke. In addition to lipid-lowering drugs, patients with hyperlipidemia are often prescribed other medications for the treatment of concomitant disease states. It is known that increases in serum cholesterol levels may lead to changes in the pharmacodynamic properties of certain drugs which are prone to bind to lipoproteins. Some of these changes may be attributable to modified drug disposition properties. Unlike other plasma proteins, lipoproteins are not

discreet protein molecules but rather sizable packages containing a variety of biological lipids (triglycerides, cholesterol and phospholipids) and specialized proteins called apoproteins. Apoproteins have functions related to lipid metabolism, providing structural integrity of the particles, and serving as ligands for tissue recognition by lipoprotein receptors. There are a number of lipoprotein receptors known to exist, and each of them differs in their expression in various tissues, apoprotein recognition, and substrates for the uptake of various lipoprotein types. Two of the most common lipoproteins are the low, and the very low lipoprotein receptors. A unique feature of drug binding to lipoproteins is that is not a simple binding phenomenon but rather an encapsulation of the drug within the lipoprotein particle. An increase in serum lipoproteins is expected to decrease the unbound fraction of the lipoprotein-bound drug in plasma, which may limit the amount of drug that would be available to enter tissues and/or be eliminated. A rodent model of hyperlipidemia has also been shown to decrease expression of some key drug metabolizing enzymes, which could further limit drug elimination. On the other hand, the lipoprotein-associated drug would be amenable to tissue uptake mediated via recognition of the lipoprotein particle by lipoprotein receptors. These two mechanisms would work against one another, thereby making it difficult to predict drug tissue levels and subsequent pharmacological effect. In our laboratory, we have studied this issue using a rodent model of hyperlipidemia, from the standpoint of tissue and plasma concentrations of drug, and the pharmacodynamic outcome. We have observed that the relative tissue uptake of some representative lipoprotein-bound drugs (halofantrine, amiodarone and cyclosporine A) varies in both a tissue and drug-specific manner. In some tissues drug concentrations increase, in others decreases or no change were observed. The levels of drug uptake into target tissues for toxic or therapeutic effect of the drugs were well correlated with measures of effect. This presentation will review the available data and discuss ramifications in drug development and clinical practice.

Engineered Lipid-Based Nanoparticles and Nanocapsules for Overcoming Multi-Drug Resistance in Cancer

Russell J. Mumper, Center for Nanotechnology in Drug Delivery, Division of Molecular Pharmaceutics, UNC Eshelman School of Pharmacy, Chapel Hill, North Carolina, USA

The Mumper lab had previously developed a novel warm microemulsion-precursor engineering process to engineer solid lipid NPs in one vessel, and the same process was recently refined to manufacture oil-filled nanocapsules. The nanocapsules were developed by experimental design, combining Taguchi array and sequential simplex optimization. The optimized BTM formula is comprised of Brij 78, and D-alpha-tocopheryl polyethylene glycol 1000 succinate, as the surfactants, and Miglyol 812 as the oil phase. BTM NPs have now been modified so that one of the many available Miglyol-type oils can be selected and used to provide optimal solubility for the selected drug of choice. Both the solid lipid drug NPs and BTM drug NPs overcome at least two ATP-dependent ABC-transport systems (MDR and MRP-associated) resulting in up to a 200-fold reduction in IC50 values in human lung, colon, ovarian, leukemia, breast, melanoma, and prostate cells. In-vivo evidence supporting the efficacy of these lipid-based NPs to address MDR in human colon, leukemia, and ovarian xenograft models has been established. For example, the Mumper lab has shown that the BTM NPs containing paclitaxel could completely inhibit the growth of Taxol-resistant NCI/ADR-RES ovarian tumors in athymic nude mice after i.v. injection. The lipid-based NPs were shown to inhibit p-glycoprotein-mediated efflux of drug and transiently deplete ATP without the empty NPs causing apoptosis. These observed effects were predominantly manifested in MDR cells as the BTM NPs were relatively non-toxic to sensitive cells and repeated injection of drug NPs or empty NPs showed no adverse gross toxicity, and multi-organ histological examination was unremarkable. The mechanism of action appears to relate to a concomitant ATP-depletion mechanism that enhances drug activity by alteration of mitochondrial respiration.

Session V a

Clinical Development of Nanomedicines

Navigating the Path to Approval with Nanomedicines: Challenges and Opportunities

Lawrence Mayer, Celator Pharmaceuticals, Vancouver, BC, Canada

Nano-scale delivery vehicles have been utilized extensively in a broad range of medical applications. The benefits provided by such "nanomedicines" can arise from reduced toxicity, increased efficacy, enhanced bioavailability, improved formulation stability or a combination of these features. However, to successfully navigate the drug development path from preclinical testing through to regulatory approval, several challenges must be met. First, the advantages afforded by the nanotechnology must fill a truly unmet medical need. In addition, the technology should minimize technical complexity in order to avoid difficulties with manufacturing and prohibitively costly products. Finally, a thorough understanding of the treatment landscape is necessary to not only project the therapeutic niche that the nanomedicine will fill if approved, but also to ensure that there is a reasonable expectation that the desired patients will be available for Phase II and Phase III clinical testing. Prospectively addressing these issues will greatly increase the likelihood of success in the clinic and also will minimize time and costs associated with drug development. Case studies will be presented to highlight how the challenges facing development of nanomedicines can be translated into opportunities for important medical advances.

Nanotechnology for Cancer Therapy: Lessons Learned from NCI's Nanotechnology Characterization Lab

Scott McNeil, SAIC-Frederick Inc./NCI at Frederick, Frederick, MD, USA

The NCI's Nanotechnology Characterization Laboratory (NCL) conducts preclinical efficacy and toxicity testing of nanoparticles intended for cancer therapeutics and diagnostics. The NCL is a collaborating partnership between the NCI, the U.S. Food and Drug Administration and the National Institute of Standards and Technology. The NCL characterizes nanoparticles' physical attributes, their in vitro biological properties, and their in vivo compatibility in animal models. The Laboratory accelerates the transition of basic nanoscale particles and devices into clinical applications by providing critical infrastructure and characterization services to nanomaterial providers, and is a national resource available to investigators from academia, industry and government. The NCL's many collaborations with nanotech investigators and expertise with a variety of nanoparticle drug delivery platforms have allowed us to elucidate trends relating physicochemical properties such as size and surface chemistry to nanoparticle behavior in biological systems, biodistribution, safety, and efficacy. This presentation will include some of the NCL's recent findings regarding nanoparticle biocompatibility and toxicity.

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Improving a Good Thing: Integrating Preclinical and Clinical Experience in the Development of Next Generation siRNA Products

Ian MacLachlan, Tekmira Pharmaceuticals Corp., Burnaby, BC, Canada

Using the modular lipid nanoparticle siRNA delivery platform known as SNALP (Stabilized Nucleic Acid Lipid Particles), Tekmira has confirmed RNAi mediated efficacy in several preclinical models of oncology, infectious and metabolic disease. Several SNALP-based product candidates are now in development and by the end of 2010 we expect there to be five SNALP based products in clinical trials. Ongoing formulation development efforts, informed by this clinical experience, continue to produce SNALP formulations with substantially increased potency and reduced toxicity. While lipid nanoparticles are

generally considered to be non-immunogenic, their *in vivo* efficacy and safety can be severely compromised due to the inherent immunostimulatory properties of their nucleic acid payloads. While the use of chemically modified siRNA with minimal immunostimulatory capacity has allowed for a more accurate delineation of the mechanism of action of siRNA based therapeutics, an essential precursor to the development of safe and effective siRNA-based drugs, recent clinical experience has suggested that even the most comprehensive battery of non-clinical testing may fail to reveal the true immune stimulatory potential of a given siRNA. Here we report new assay methodology that more completely reflects the clinical response to siRNA drugs, allowing for the elucidation of previously cryptic immune stimulatory activity and redesign of siRNA drug substances that are immune silent. Approaches towards the integration of these improvements into new and ongoing product development efforts will be discussed.

Regulatory and Scientific Approaches for Nanomedicines

Raimar Löbenberg1*, Wilson H Roa2, Warren H Finaly3 and Elmar Prenner4, 1) Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, AB, Canada; 2) Department of Oncology, Cross Cancer Institute, University of Alberta, Edmonton, AB; 3) Department of Mechanical Engineering, University of Alberta, Aerosol Research Laboratory of Alberta, Edmonton, AB; 4) Department of Biological Sciences, Division of Biochemistry; University of Calgary, Calgary, AB, Canada.

Nano-technology can be considered a new frontier in biomedical sciences. Nano-sized drug delivery systems are an emerging field in biomedical sciences. Delivery systems in the nanometer range are very promising drug carriers due to their ability to overcome many limitations associated with conventional drug delivery systems including multi drug resistance in cancer treatment. Advances in dry powder inhalers and the development of suitable carriers for nano-medical drug delivery systems enable the application of nano-medical treatment strategies to the pulmonary route of administration. The talk will show strategies for the delivery of nanoparticles to the lungs and how an active release mechanism can be added to carrier particles. Any interaction between the nano-medical device and the lung surfaces has to be carefully assessed. Strategies to evaluate nanotoxicological aspects between nanoparticles and the lungs surfactants will be discussed. The cytotoxicity and cellular uptake of doxorubicin loaded nanoparticles using macrophages and lung cancer cells was investigated. After being phagocytosed, inhalable NPs have the ability to induce certain changes in alveolar macrophages to trigger cytokine release. This acute inflammation might have important implications in the treatment of lung cancer.

An animal study using inhalable nanoparticles will be presented. Doxorubicin-loaded nanoparticles were incorporated into inhalable effervescent carrier particles using a spray-freeze-drying technique. The prepared effervescent inhalable powder was tested in a tumor bearing Balb/c mice model. As controls, animals were treated with blank inhalable nanoparticle powder or injections of doxorubicin nanoparticle, doxorubicin solution or saline via the tail vein. Kaplan-Meier curves were plotted for survival times in different groups. The results demonstrated that animals treated with effervescent doxorubicin nanoparticle powder which contained 30 µg doxorubicin showed improved survival times during the course of the study compared to all other controls. More than 80% of the animals survived for more than 90 days and 70% for more than 140 days. In the control group which was treated with 30 µg doxorubicin solution or doxorubicin nanoparticles as i.v. injection (equal to the drug content of 1 mg nanoparticle powder), all the mice died within less than 50 days. The pathological samples showed large tumor masses in the lungs of those animals not treated or treated with iv injection of doxorubicin nanoparticles or solution. The tested powder showed more efficiency compared to the intravenous injection of doxorubicin solution and doxorubicin nanoparticle suspension in vivo.

The application of nano-medical strategies to the pulmonary route of administration has the potential to treat lung specific diseases locally and to overcome current treatment limitation associated with other routes of administration. The development of effervescent inhalable nanoparticles loaded with bioactive molecules is a new delivery platform, which may allow the targeting of lung specific diseases in the future.

Session V b

Technical and Regulatory Issues for the Bioanalytical Laboratory

Recent Scientific and Regulatory Developments in Preclinical and Clinical Bioanalytical Data Supporting GLP

Xiaowei (Shirley) Teng, BRI Biopharmaceutical Research Inc. Vancouver, BC, Canada

Regulatory and scientific issues are inseparable topics governing the best practices in the measurement of drugs and metabolites in biological fluids, supporting pre-clinical and clinical pharmacokinetics and drug metabolism studies. This presentation will review current best practices in the development and validation of LC/MS/MS assays supporting small molecule development. Examples will be cited to demonstrate the entire analytical process beginning with sample collection and handling at the clinic, to sample storage, assay procedures and data reduction. The design and practice of this analytical process is an "exact science" potentially plagued with hidden "silent errors".

Health Canada and SCC Memorandum of Understanding-A Brief Overview of The Canadian GLP Program

Vesna Janic, GLP Inspector for SCC, Vancouver, BC

On April 30, 2010, Health Canada released the finalized *Guidance Document Non-Clinical Laboratory Study Data Supporting Drug Product Applications and Submissions: Adherence to Good Laboratory Practice*. This presentation will provide a brief overview of Canada's international obligations to GLP compliance, the Canadian GLP Inspection Program, and the implications to the pharmaceutical industry.

Canada, as a member country of the Organization for Economic Cooperation and Development (OECD), has the obligation to establish national procedures for monitoring Good Laboratory Practice (GLP) compliance, designate a GLP Monitoring Authority, and require test facilities to issue a GLP compliance declaration. By signing a Memorandum of Understanding with the Standards Council of Canada (SCC) as the GLP Monitoring Authority, Health Canada has fulfilled this obligation.

SCC is an internationally recognized Canadian GLP Monitoring Authority. Under the SCC GLP inspection program, facility and study inspections are conducted every two years. GLP compliance is assessed against OECD Principles of GLP. The purpose of GLP compliance is to promote the quality and validity of test data and improve the international acceptance of that data. A brief overview of the Canadian GLP inspection program will be presented, including how to apply for SCC inspection, what documentation is required for GLP compliance, and what to expect during the inspection process for GLP recognition.

Health Canada expects that sponsors will consult ICH (International Conference on Harmonisation) guidelines and determine which studies should be performed under GLP. These studies are expected to be conducted in accordance with the OECD Principles of GLP, effective immediately. However, Health Canada acknowledges that it will take some time for facilities to comply with the newly released guidance document; therefore facilities have one year to obtain their GLP Recognition Certificate. By May 1, 2011, all Canadian facilities conducting GLP studies for submission to OECD member countries must be GLP recognized by the SCC. Not only will this impact your data submissions to Health Canada, but it will impact submissions to other OECD member countries as well.

Challenges in Regulated Bioanalysis - A Case Study

Sanj Devarajan, Clinical Development, ratiopharm inc., Mississauga, ON, Canada

The field of bioanalysis has changed quickly over the past 20 years. So too, international agencies have made significant progress in keeping up with

this rapid change. In this increasingly regulated environment, bioanalytical scientists face challenges and unexpected events during method validation or routine sample analysis. These data may be submitted to an agency for review, and therefore must support the integrity of sample analysis. Using actual case-study data, this presentation highlights some challenges faced during and after sample analysis.

Quality Management System for Bioanalysis Supporting Clinical Trials

Nageshwar R. Thudi, Group Leader, Ranbaxy Pharmaceuticals, Mississauga, ON, Canada

In order to standardize the quality management system (QMS) for laboratories conducting Bioanalysis in support of clinical trials, in 2008 a working group from sponsor based companies has been formed. The working group has made several conference calls and summarized below few issues.

- QMS is inconsistent across laboratories, even between geographic locations within the same organization.
- FDA is establishing standards by 483's.
- Do not want Bioanalysis conducted under full cGMP.
- DSI challenging integrity of results not generated according to the principles of current guidelines (e.g. ICH Q10, FDA Guideline for QMS Approach to Pharmaceutical cGMP).
- Absence of an industry established standard. This results in increased costs to achieve zero risk or sliding more towards full cGMP.
- Burden remains with ***sponsor*** to establish criteria and verify compliance and reliability.

By considering above points, working group developed a QMS based

- On the best practices of GLP, GMP and ICH and not a reflex response.
- Ensure the QMS meets current ***regulatory*** expectations for reliability, accuracy and integrity.
- Ensure that QMS meets the ***industry*** expectation for effectiveness

Latest document has been submitted to the FDA (Division of Dockets Management) as a level 1 guidance document (Docket No. FDA-2009-D-0428)

In summary BQSI Team Proposes

- Quality Manual and Policy along with description of the organization (ICHQ10)
- Quality Management (section 2.0)
- Personnel and Training (section 3.0)
- Facilities and Equipment (sections 4.0 & 5.0)
- Study Execution (sections 8, 11, 12, 18)
- Study Execution (sections 8, 11, 12, 18)Change Management Programs (section 13)
- Complaint Programs (section 15)
- Provide more consistent assessment and enforcement by the FDA or EU Regulatory
- Third party assessment assuring greater likelihood of data and study reliability
- Reduce or eliminate costs and uncertainty associated with zero risk approach and avoid the "Slippery Slope" of full cGMP
- Potentially reduce registration approval cycle due to reduced issues and concerns related to bioanalytical studies.

Session VI

Challenge on How to Align Pharmaceutical Development with Payor and Consumer Needs

The Need to Take on the Challenge of Alignment of Pharma with Payor Needs

Suzanne C. Malfair Taylor, Drug Use Optimization, Pharmaceutical Services Division, BC Ministry of Health Services, Vancouver, BC

Pharmaceutical development should be aligned with the needs of payers for drugs that address unmet or under-met clinical needs. Effective alignment would help to ensure that scarce resources are invested in those products that provide the most value to society. Indeed, the needs of payers and Pharma are not that different. The balance between meeting the payers' fiscal needs and Pharma's return on investment needs to be found. Through ongoing dialogue and cooperation, Pharma will be able to focus on producing drugs that provide drugs that show tangible advances and improved health outcomes. Innovation and alignment would be rewarded through streamlined processes, formulary access and price considerations.

The Need to Take on the Challenge of Alignment of Pharma with Payer Needs – The Pharmacist Perspective

Marnie Mitchell, CEO, British Columbia Pharmacy Association, Vancouver, British Columbia

Pharmacists are at the front line of delivery of pharmaceutical care. Increasingly they are playing a larger role in the choice of therapy. They are always playing a central role in dealing with patients on the accessibility and affordability of medication options. They deal constantly with listing choices made by payers – is the drug a benefit or not? And if it is a benefit, are there conditions in terms of patient characteristics or therapies already tried?

The pharmacist perspective will be considered from a number of angles – pharmacist as scientist; pharmacist as health care provider; pharmacist as part of a private sector business operation. The pharmacist as scientist considers the evidence for the possible drug choices; whether that evidence is compelling or not; and how that evidence may relate to a specific patient. The pharmacist as health care provider considers what the patient and prescriber needs/wants; how the features of the therapeutic options might affect adherence/persistence with the therapy; and what the patient can afford, or is willing to pay. The pharmacist as part of a private sector business operation considers how much time/effort is required of them to obtain/maintain drug plan coverage for this patient for this drug; what are the drug plan rules for providing coverage; and what is the risk the pharmacy will not be reimbursed by the plan.

Challenge on How to Align Pharmaceutical Development with Payor and Consumer Needs - Payor Perspective

Leza Muir, Claims Services, Pacific Blue Cross, Vancouver BC.

Pharmaceutical spending in Canada is the second largest health care expense, and growing at more than 10% each year according to Canadian Institute for Health Information (CIHI). With a total health care spend of $26.9 billion in 2007, 54% of individuals are covered by private insurance, accounting for 35% of the total drug expenditures. While the average price of a prescription has not increased; the utilization of drugs has increased with more options being available.

In British Columbia in 2008, employers and unions provided health insurance protection for over 2.7 million residents and sponsored private plan benefits that totaled over $2.2 billion for medical, hospital, dental and drug coverage. Prescription drugs account for 70% of the cost of the private health care costs. Prescription drugs play a valuable and cost effective role in our overall healthcare system. New drug innovations, and compliance with a medication regime often avoids more costly absenteeism, loss of

productivity, hospitalization and disability. As private healthcare costs continue to rise, the escalating cost of drugs in particular not only threatens consumer health outcomes when patients can no longer afford medication; it also puts drug plans at risk when employers and employees can no longer afford the increasing premiums.
It is a complex system, with numerous issues. Pacific Blue Cross is continuing to work collaboratively to find sustainable solutions that work for all stakeholders alike.

Payor-Sponsor Scientific Dialogue

Mark Ferdinand, Canada's Research-Based Pharmaceutical Companies (Rx&D), Ottawa, ON

The process (which we will call "Early Scientific Dialogue") that has long characterized the discussion and exchange of scientific knowledge between academics, sponsors/pharmaceutical manufacturers, and national market authorization regulators globally, such as the International Conference on Harmonization (ICH), does not exist in the same formal and regularized manner between sponsors/pharmaceutical manufacturers and payors (with some notable exceptions: while it may be said that some pharmaceutical manufacturers in Canada do engage in early discussions with payors at around the time of Global Phase IIb trials, this is the exception and not the rule.)

Furthermore, despite the fact that some form of economic assessment of medicines have been a mainstay of new drug reimbursement decision making for the better part of 30+ years in Canada, it is a wonder that some effort to standardize the scientific interaction between payors and sponsors has not yet taken hold in a meaningful way (with full recognition for the resource and scientific challenges this would bring).

During my short presentation, I would like to introduce the questions asked by various actors in the various steps in the "drug decision-maker chain". It is our belief that various actors in the decision-making chain can either
- put into question previous scientific evaluation(s) (e.g. use of comparators in assessments); or
- not explicitly weight the factors involved in their decision-making or make transparent how a decision was arrived at to provide public coverage for a new drug.

I will suggest that there is a need for greater understanding of each step in the decision maker chain…by each of the decision-makers. Only then, will it be possible for all relevant actors to evolve to a second phase of creating a framework for earlier scientific dialogue between payors and pharmaceutical manufacturers, with the aim of creating a more patient-centred and predictable pathway for new health technologies.

Through a Glass Darkly – The Future of Pharma

Mervyn J. Turner, Merck & Co., Inc., and SVP Emerging Markets, Merck Research Laboratories, Rahway, NJ, USA

The physicist Niels Bohr is said to have commented that "prediction is very difficult, especially about the future". This statement aptly sums up the conundrum for drug discoverers and developers, faced with a fifteen year lag between the start of a program and entry into the marketplace – if the program survives! What part of the global economy stands still for that length of time in today's world? What kind of healthcare ecosystem will our products be entering? Increasingly, late stage development discontinuations are ascribed to "strategic reasons", a term that frequently masks a mismatch between product attributes and the needs of the marketplace. At Merck, we have used Scenario Planning to try to challenge our views about what the world will look like in the future, and what the implications might be for our global strategy. What businesses should we be in? And where? What kind of demands will be placed on our products in order to get reimbursement? Who will be paying? The answers have major implications for the way in which we deploy our resources and manage a portfolio of risk. At a time when R&D organizations across the industry are struggling to generate a reasonable return on invested capital, addressing these issues successfully will be a major determinant of long term success.

Speaker Biographies

Christine Allen
Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, ON, Canada

Christine Allen is an Associate Professor in the Leslie Dan Faculty of Pharmacy at the University of Toronto. She is cross-appointed in the Departments of Chemistry, Chemical Engineering and Applied Chemistry and the Institute of Biomaterials and Biomedical Engineering. Her research is focused on the rational design and development of new materials and technologies for the delivery of drugs and contrast agents (Lab Website: http://phm.utoronto.ca/~allen/). Allen completed her doctoral research in the Department of Chemistry at McGill University and post-doctoral research in the Department of Advanced Therapeutics at the B.C. Cancer Agency. She joined University of Toronto in 2002, from Celator Pharmaceuticals Inc. (Vancouver, B.C.) where she had worked as a scientist and Assistant Director of materials research. She has over 60 publications, numerous patent applications, and seven book chapters on both lipid and polymer-based delivery systems. She has served on several peer review panels for granting agencies including CIHR (2004, 2005-2009), NCIC (2005, 2006) and NIH (2006, 2008, 2010). In 2004, she was awarded a CIHR-Rx&D Career Award (2004-2009) for her research on the design and development of technologies for cancer treatment. In 2006, she was awarded the Association of Faculties of Pharmacy of Canada/AstraZeneca New Investigator Research Award and the Canadian Society Pharmaceutical Science/GlaxoSmithKline Early Career Award. She is involved in numerous scientific societies or organizations including elected member of the scientific advisory board CRS, Vice-President Canadian Chapter-CRS, member of the board of directors CSPS and member of the annual organizing committee NanoDDS. She is a member of the editorial boards for Bioconjugate Chemistry and Drug Delivery.

Mansoor M. Amiji
Department of Pharmaceutical Sciences, and Nanomedicine Education and Research Consortium (NERC), Northeastern University, Boston, MA, USA

Dr. Mansoor Amiji is Distinguished Professor and Chair of the Pharmaceutical Sciences Department in the School of Pharmacy at Northeastern University in Boston. He is also the Co-Director of the Nanomedicine Education and Research Consortium (NERC). NERC oversees a doctoral training program in Nanomedicine Science and Technology that is co-funded by the NIH and NSF.

Dr. Amiji received his undergraduate degree in pharmacy from Northeastern University in 1988 and his Ph.D. in pharmaceutics from Purdue University in 1992. His areas of specialization include polymeric biomaterials, advanced drug delivery systems, and nanomedical technologies. He has three published books, *Applied Physical Pharmacy* (McGraw-Hill, 2003) and *Polymeric Gene Delivery: Principles and Applications* (Taylor & Francis, 2005) and *Nanotechnology for Cancer Therapy* (Taylor & Francis, 2007), along with over 150 published articles and conference proceedings. Dr. Amiji has received sustained funding from the National Institutes of Health, National Science Foundation, other foundations, and private companies to support research activities in his laboratory. He is also an inventor of over 10 U.S. utility patent or patent applications. Dr. Amiji has received a number of awards including the 2007 American Association of Pharmaceutical Scientist's (AAPS) Meritorious Manuscript Award and the AAPS Fellowship.

Marcel B. Bally
BC Cancer Agency; Faculty of Medicine (UBC); Faculty of Pharmaceutical Sciences (UBC) and Division of Pharmacology and Toxicology (Centre for Drug Research and Development), Vancouver, BC, Canada

Dr. Bally's research interests focus on the development and characterization of novel lipid-based nanopharmaceuticals (LNs) for use in the treatment of cancer. The diversity of his funded projects and collaborations reflect opportunities to purse development of an assortment of lipid-based drug carrier technologies as well as explore a number of therapeutic strategies involving the use of established approved anti-cancer drugs, novel molecularly targeted drugs (e.g. small molecules, antisense oligonucleotides, siRNA), gene therapy and immunotherapy. Dr. Bally is the Co-leader (along with Dr. Karen Gelmon) of Experimental Therapeutics, a translational research team within the BC Cancer Agency. At the Vancouver Research Centre Site Experimental Therapeutics operates the Investigational Drug Program (IDP), a business unit

that supports a number of academic and industrial collaborations, serves as a GLP and GMP manufacturing and analytical lab for early stage products destined for use in GLP toxicology studies and early phase clinical trials, hopefully to be conducted at the BC Cancer Agency. Dr. Bally is currently Head of the Division of Pharmacology and Toxicology within British Columbia's Center for Drug Research and Development (CDRD; www.cdrd.ca); an organization aimed at addressing the growing commercialization gap between medical discoveries from academia and the opportunity to obtain investments to support late stage preclinical, clinical and the commercial development of the technology. In this context Dr. Bally is focused primarily in two areas: i) development of CDRD's Drug Research Institute at the BC Cancer Agency (DRI-BCCA) and (ii) facilitation of broader access to the pharmacology capabilities within CDRD to support drug development for cancer as well as non-cancer indications. He helps to support the organization's efforts in drug evaluation in animal models of disease and to define the critical proof-of-concept data needed to support further development of promising technologies.

Anahita Bhathena
Pharmacogenetics, Abbott Labs, Abbott Park, Illinois, USA

Dr. Anahita Bhathena is Group Leader for the Pharmacogenetics department at Abbott. She received her Bachelor's degree in Toxicology and a Ph.D. in Pharmacology from the University of Toronto, Faculty of Medicine. Her Ph.D. research examined the regulation of gene expression by aromatic hydrocarbons. Following her Ph.D., Anahita trained as a Post Doctoral Research Fellow in the Division of Pediatric Clinical and Developmental Pharmacology at the Children's Mercy Hospital in Kansas City, where she worked on the pharmacogenetics of drug metabolism and transport. Anahita's research is focused on improving the use of therapeutics by incorporating knowledge about underlying genetic variability which may affect drug response in patients. In her current position Anahita works on pharmacogenetic studies in clinical trials to facilitate and support the drug development process.

Ron Boch
Variation Biotechnologies Inc., Ottawa, ON

Dr. Ron Boch is the Director, Pharmaceutical Development at Variation Biotechnologies Inc. where he is responsible for CMC and formulation. For over ten years, Dr. Boch worked at QLT Inc. where he was the Associate Director, Formulation. While at QLT, he contributed to the development of Visudyne and was responsible for establishing and leading a formulation team developing preclinical and clinical products. Dr. Boch is a named inventor of eight patent families with more than sixty US and international patents and patent applications filed. In addition to his contributions in industry, Dr. Boch was an Honorary Research Associate and NSERC Industrial Research Fellow in the Department of Chemistry at the University of British Columbia. Dr. Boch obtained his Ph.D. degree in Chemistry and a B.Sc. in Biochemistry at the University of Ottawa.

Dion Brocks
Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, AB, Canada

Dion Brocks is a Professor and Associate Dean of undergraduate studies in the Faculty of Pharmacy and Pharmaceutical Sciences at the University of Alberta. Prior to commencing his academic career, Dr. Brocks worked as in hospital and community pharmacies in Alberta. After receipt of his M.Pharm. degree in clinical pharmacy in 1986, he served as Clinical Coordinator at the Rockyview Hospital Pharmacy department in Calgary. He received his doctoral degree in Pharmaceutical Sciences under the supervision of Dr. F. Jamali, specializing in Pharmacokinetics, from the University of Alberta in 1993. He was employed by the Department of Drug Metabolism and Pharmacokinetics at SmithKline Beecham Pharmaceutical from 1993 to late 1995, after which he took a position as Assistant Professor at the University of Saskatchewan. In 1998, he joined the faculty at the Western University of Health Sciences in Pomona CA (suburban Los Angeles) as Associate Professor of Pharmaceutical Sciences. He taught pharmacokinetics and pursued his research interests there involving stereoselective pharmacokinetics of halofantrine until January 2002, when he returned to his alma mater as Associate Professor of Pharmaceutical Sciences. Dr. Brocks has published over 83 peer-reviewed manuscripts related to pharmacokinetics, and has authored

numerous published abstracts and some book chapters. He is a member of the editorial board of the Journal of Clinical Pharmacology and Biopharmaceutics and Drug Disposition, and is Managing Editor of the Journal of Pharmacy & Pharmaceutical Sciences. His primary research interest is directed towards understanding the influence of lipids and hyperlipidemia on the kinetics and dynamics of lipoprotein-bound drugs. His interest also include the relationship between CYP1A1 and drug-induced pulmonary toxicity, the effect of obesity on pharmacokinetics of drugs, and pharmacokinetics drugs after encapsulation into some novel formulation developed by his colleague Dr. A. Lavasanifar.

Pieter Cullis
University of British Columbia/CDRD, Vancouver, BC

Pieter R. Cullis, Ph.D., is Founding Scientific Director, Centre for Drug Research and Development and Professor, Department of Biochemistry and Molecular Biology, University of British Columbia. Dr. Cullis' laboratory has been responsible for fundamental advances in the generation, loading and targeting of liposomal nanoparticulate (LNP) systems for intravenous delivery of conventional and genetic drugs. This work has contributed to two LNP products that have been approved by regulatory agencies in the U.S. and Europe for the treatment of cancer and its complications, another that is in late stage clinical trials for the treatment of acute lymphocytic leukemia and four more that are in Phase I clinical studies. Dr. Cullis co-founded The Canadian Liposome Company, Inex Pharmaceuticals (now Tekmira Pharmaceuticals), Lipex Biomembranes Inc., Northern Lipids Inc., Protiva Biotherapeutics and, most recently, AlCana Technologies. He has published over 280 scientific articles and is an inventor on over 35 patents. Dr. Cullis has received many awards, including the B.C. Science Council Gold Medal for Health Sciences in 1991, the Alec D. Bangham Award for contributions to liposome science and technology in 2000 and the B.C. Biotechnology Association award for Innovation and Achievement in 2002. He was elected a Fellow of the Royal Society of Canada in 2004.

Carolyn Cummins
Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, ON, Canada

Carolyn Cummins is an Assistant Professor in the Faculty of Pharmacy at the University of Toronto. She completed her undergraduate degree in chemistry at McGill University and her Ph.D. in pharmaceutical chemistry at the University of California San Francisco. During her postdoctoral training with David Mangelsdorf at the University of Texas Southwestern Medical Center she gained molecular biology, in vivo biology, and receptor pharmacology experience in the area of nuclear hormone receptors. By combining knowledge of P450 metabolism and LC/MS, she helped identify the first known ligand for a nuclear receptor in *C. elegans*. She further discovered that the nuclear receptor LXRalpha regulates a key protein important for regulation of glucocorticoid synthesis. Because LXR is activated by metabolites of cholesterol, these results have provided a direct link between dietary cholesterol and stress hormone synthesis. Her independent research program continues to focus on the study of nuclear hormone receptors and their impact on metabolic disease.

Sanj Devarajan
Clinical Development, ratiopharm inc., Mississauga, ON

Sanj Devarajan is the Senior Manager of the Clinical Development Department at ratiopharm, a pharmaceutical company located in Mississauga, Canada. In this role, he provides scientific guidance for the bioanalytical activities related to all bioequivalence studies performed worldwide by ratiopharm. His work contributes to generic drug approvals in Canada, United States and Europe. He is also closely involved in helping to identify and evaluate future drug product opportunities for ratiopharm's development pipeline.

Sanj has been closely involved in regulated bioanalysis over the past 20 years in a variety of roles involving sample extraction, method development/optimization, and method validation to Study Director.

In the past, he held leadership positions at several international pharmaceutical companies (Sanofi-Aventis, Taro, Genpharm, Merck Generics, Mylan), and Contract Research Organizations (Maxxam Analytics, Pharma Medica) in Canada and the United Kingdom.

Within his current position at ratiopharm, Sanj continues to provide his expertise, perspective, regulatory support and collaboration to bioanalytical scientists at Contract Research Organizations world-wide.

Sanj is a graduate of the University of Surrey, United Kingdom. He obtained a Bachelors of Science, Biochemistry (Medical) in 1991.

In his spare time, Sanj is an avid squash player and likes to keep fit. As well, Sanj continues to seek enlightenment through meditation and spiritual philosophy.

Laszlo Endrenyi
University of Toronto, Toronto, ON

Dr. 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 has received several recognitions, including an honorary doctorate from Semmelweis University. Externally, he has served on grant review committees and on editorial boards of research journals including the Amer. J. Physiol, J. Pharmacokin. Pharmacodyn., J. Pharm. Pharm. Sci., and J. Pharm. Sci. He published a book on Kinetic Data Analysis and over 160 research papers. Several of these established principles for the design and analysis of enzyme and pharmacokinetic investigations. More recently, he extensively developed principles and applications for the evaluation of bioavailability and bioequivalence. His studies were instrumental in the adoption of some regulations and the withdrawals of others. He has consulted with the Food and Drug Administration and the Canadian Health Protection Branch 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 and bioequivalence studies.

Mark Ferdinand
Policy Research & Analysis, Rx&D, Ottawa, ON

Mark Ferdinand is Vice President of Policy Research & Analysis, leading pharmaceutical, health and economic policy development at Rx&D. Between 2005 and 2009, Mark was Vice President, Policy, Research, Regulatory and Scientific Affairs at Rx&D. Prior to assuming this role, he served as Rx&D's Director of Policy Development.

Before working at Rx&D, Mark advised senior federal Cabinet Ministers in both the Chrétien and Martin governments, and also worked as a federal public servant in the fields of Cabinet Affairs, economic and social policy development at the Atlantic Canada Opportunities Agency (ACOA), Human Resources Development Canada (HRDC), and Citizenship and Immigration Canada (CIC).

Mark started his professional career as a public servant at the Office of the Commissioner of Official Languages (OCOL). Mark is a graduate of the Faculty of Law of the University of Montreal and holds a Bachelor degree (First Class Honours) in Italian from McGill University.

During a long history of local volunteerism, Mark has served various constituencies, most recently as a member of the Advisory Committee of the Quebec Educational Mathematics and Science Alignment Project (2007-2009) and as a member and then Chairperson of the Board of Directors of a community-based Legal Aid Clinic in Ottawa (1999-2003).

Brian C. Foster
Health Canada, Ottawa, ON, Canada

Dr. Foster (Ph.D. Medicinal Chemistry, University of Alberta) is a Senior Science Advisor in the Office of Science, Therapeutic Products Directorate, Health Canada and an Adjunct Professor, Department of Cellular and Molecular Medicine, Faculty of Medicine, University of Ottawa.

His research interests include alternative models for drug interactions and disposition. Since joining Health Canada, his research has been in the area of drug metabolism, pharmacogenetics, and how natural health products or other xenobiotics affect the safety and efficacy of conventional therapeutic products. He has published 76 refereed articles and reviews, and has been an invited speaker at many conferences. He currently has 4 graduate students in a joint Health Canada - University of Ottawa Centre for Research in Biopharmaceuticals and Biotechnology laboratory.

David W. Grainger
Department of Pharmaceutics and Pharmaceutical Chemistry, University of Utah, Salt Lake City, UT, USA

David W. Grainger is the *George S. and Dolores Doré Eccles Presidential Endowed Chair in*

Pharmaceutics and Pharmaceutical Chemistry, Chair, Department of Pharmaceutics and Pharmaceutical Chemistry, and Professor of Bioengineering at University of Utah. Grainger's expertise is focused on various aspects of materials in medicine, including improving implanted medical device performance, drug delivery of therapeutic proteins, siRNA, and live vaccines, nanomaterials interactions with human tissues, and innovating diagnostic devices based on DNA and protein biomarker capture. Grainger has training in synthetic, analytical and biophysical chemistry, and experience with biotechnology and medical devices in many applications. Grainger has >130 full research publications, organized 21 international scientific symposia, presented over 320 invited lectures all over the world. He serves on the editorial boards for the major biomaterials and drug delivery journals in the field and reviews over 60 manuscripts annually. He also is a scientific advisory board member for several national biomedical research centers in the United States, in Europe and in Asia. Grainger has helped found three medical device companies, and sits on Scientific Advisory boards for 4 biomedical companies, and actively consults internationally with industries in applications of materials in biotechnologies and medicine.

Michael Hope
AlCana Technologies, Vancouver, BC and Visiting Scientist, Department of Biochemistry and Molecular Biology, University of British Columbia, Vancouver, BC, Canada

Dr. Hope (PhD, University of London, UK) is Chief Scientific Officer of AlCana Technologies. He has more than 30 years of research and development experience with a special interest in the roles of lipids in membrane structure and function and the application of liposomes and lipid-based technology to drug delivery. He has more than 100 publications in the field and whilst holding senior scientific and management positions in the Canadian Liposome Company, Inex Pharmaceuticals and Tekmira Pharmaceuticals Dr. Hope was involved in the discovery and development of a number of lipid-based drug delivery systems from bench to the clinic. These include a lipid formulation of amphotericin B (Abelcet®), and liposome encapsulated formulations of doxorubicin (Myocet®), vincristine (Marqibo®), topotecan (Brakiva™), vinorelbine (Alocrest™) and ciprofloxacin as well intravenous liposome technology to reverse atherosclerosis. In recent years Dr. Hope has focused on the development of lipid nanoparticles for in vivo delivery of nucleic acid oligonucleotide drugs, in particular antisense, CpG immune stimulatory sequences and siRNA.

Leaf Huang
Eshelman School of Pharmacy, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

Leaf Huang, Ph.D., is the Fred N. Eshelman Distinguished Professor and Chair, Division of Molecular Pharmaceutics in the Eshelman School of Pharmacy, University of North Carolina at Chapel Hill. Dr. Huang's research has been in the area of gene therapy and targeted drug delivery. He has pioneered the liposome non-viral vector and has produced the vector for the first non-viral clinical trial in 1992. His current work centers on further improvement of liposome vectors for gene transfer in tumor, liver and lung. He also continues research in establishing a ligand targeted delivery system for **siRNA** and **peptides** for tumor growth inhibition and for peptide **vaccines** in treating cervical cancer. He has authored or co-authored more than 300 peer-reviewed papers and more than 120 reviews and book chapters. He is also the inventor or co-inventor of 16 US and foreign patents. In 2004, he received the Alec D. Bangham MD FRS Achievement Award, which is highest honor in the field of liposome research. Dr. Huang has also co-founded 4 biotech start-ups in the past.

Vesna Janic
GLP Inspector for SCC, Vancouver, BC, Canada

Vesna Janic is certified by the Society of Quality Assurance (SQA) as a Registered Quality Assurance Professional in GLP (RQAP–GLP). She is also a registered GLP Inspector with SCC and holds a Bachelor of Science degree in Biology.

Most recently, she was the Director of Corporate Quality Assurance at CANTEST, where she was responsible for establishing and maintaining the harmonized corporate quality system compliant with OECD, EPA and FDA GLP, HC and US cGMP, GCP and ISO/IEC 17025. Her expertise is in laboratory compliance with regulations and conformance with standards, not limited to: providing regulatory direction; representing companies during all quality and regulatory inspections; conducting facility and study audits;

performing gap analysis; setting up CAPA systems; providing GxP and ISO training; conducting vendor qualifications; managing document control and archiving. Prior to her over 10 years of QA experience, Vesna was part of the R&D Group at BC Research where her research supported 3 patent applications, one directly as co-inventor.

Vesna is a member of BC Chapter of Regulatory Affairs Professional Society, Society of Quality Assurance and Bioanalytical Specialty Section of SQA and has years of professional education from RAPs, SQA, ASQ, CSPS, SCC, CALA and various leadership training providers.

Athena Juneson
Quaveo Management Consultants, Vancouver, BC

Athena Juneson is the Vice President of Project Management Consulting at Quaveo Management Consultants and is responsible for the life-cycle management of multi-functional projects. Prior to Quaveo, Athena was responsible for identifying and developing relationships with new and existing clients, planning and coordinating all sales activities related to the pharmaceutical operations, participating in networking and conference activities and keeping abreast of developments in both the domestic and international business arenas as a Manager of Business Development at Maxxam Analytics International Corporation.

Athena has also worked as a Senior Project Manager for CANTEST Ltd. for five years where she led a team of Project Managers for the Pharmaceutical Operations and helped with multiple team integrations and implemented a new project management process within the division. She was also a Project Manager at Inex Pharmaceuticals. Athena is experienced with managing time, cost, resources and quality as well as controlling change, analyzing risk, identifying issues, increasing client acceptance and streamlining communications.

Athena completed her B.Sc. from the University of British Columbia in Genetics and Cell Biology and has a Project Management Professional (PMP) certification from the Project Management Institute.

David Kwok
BRI Biopharmaceutical Research Inc., Vancouver, BC, Canada

Dr. David Kwok is President & CEO, BRI Biopharmaceutical Research Inc. Dr. Kwok has worked in the analytical and bioanalytical field for over 20 years providing LC/MS/MS and DM/PK contract research services to the pharmaceutical and biotechnology companies in discovery, preclinical and clinical programs.

He received his Ph.D. in medicinal chemistry in 1991 from the pharmacy program at the University of British Columbia, Canada. He served in a variety of scientific and management positions at Health Canada from 1991 to 1998 responsible for designing analytical assays in support of botanical drug safety and quality control, anti-microbial drug resistance and veterinary drugs laboratory programs.

In 1998 Dr. Kwok founded BRI Biopharmaceutical Research Inc. with the mission to provide enabling LC/MS/MS bioanalytical chemistry, CMC analytical chemistry and DM/PK contract research services to integrate discovery, pre-clinical and clinical development.

Dr. Kwok is the co-founder of BRIVAL™ lead by Dr. Albert Li and Ms. Clara Faan to provide a full spectrum of *in vitro* drug metabolism contract research services specializing in the use of primary human hepatocytes. Dr. Kwok also co-founded Oncograph™ lead by Dr. Yuzhuo Wang and Dr. Hui Xue, both world renown for their development of a patient-derived primary tumor xenograft model to better predict anticancer drug sensitivity for individual patient.

Dr. Kwok is the holder of several US patents and has contributed to over 30 scientific publications in bioanalytical mass spectrometry applications and pre-clinical drug candidate optimization studies in peer-reviewed journals, poster presentations, and scientific review journals.

Afsaneh Lavasanifar
Faculty of Pharmacy & Pharmaceutical Sciences, University of Alberta, Edmonton, AB, Canada

Dr Lavasanifar is an Associate Professor in the Faculty of Pharmacy and Pharmaceutical Sciences of the University of Alberta. She has completed her undergraduate Pharm. D. degree from Faculty of Pharmacy, Tehran University of Medical Sciences, Iran and obtained her PhD in Pharmaceutical Sciences from Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta. Her research is focused on the design and development of polymer based delivery systems that can increase solubility, modify the pharmacokinetic pattern, reduce toxicity and increase the efficacy of different therapeutic agents. The ongoing research projects in her laboratory include development of polymeric

nano-carriers as systemic and regional delivery systems for cancer chemo/immunotherapy and development of stimulus responsive nano-gels for skin regeneration and treatment of hypertrophic scarring and fibrosis. Dr Lavasanifar has more than 60 peer reviewed published/in press manuscripts in highly ranked journals in pharmaceutical sciences, 2 book chapters, several abstracts and numerous conference presentations. Two of her papers have been recognized as the top three and ten cited paper in Journal of Pharmaceutical Sciences and Journal of Controlled Release, respectively. She is an inventor in 5 patent/patent applications on novel polymer based formulations for drug and siRNA delivery. She has been the recipient of the 2007GlaxoSmithKline/CSPS Early Career Award and the 2009 Sanofi-Aventis/AFPC award in recognition of outstanding research in Pharmacy as a new investigator. She has an active teaching program in both undergraduate and graduate levels in the area of pharmaceutics and nanotechnology for drug delivery.

Raimar Löbenberg
Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, AB, Canada

Dr. Löbenberg holds a BS in pharmacy from the Johannes Gutenberg-University in Mainz, Germany. He received his PhD in pharmaceutics from the Johann Wolfgang Goethe-University in Frankfurt in 1996. He worked on the fundamentals of the Biopharmaceutical Drug Classification System (BSC). He joined the University of Alberta in 2000. His research interests are in dissolution testing to predict the oral performance of dosage forms and in Biopharmaceutics. In recent years, he has consulted different pharmaceutical and nutraceutical companies in their product development and helped them to set product specifications according to the BCS.

The application of nanotechnology for drug delivery is another major research interest. Here Dr. Löbenberg investigates the pulmonary delivery of drug loaded nanoparticles to treat diseases like lung cancer.

He is the representative of the Association of Faculties of Pharmacy in Canada to the USP Convention; he is member of the USP Dietary Supplement Expert Committee and member of the USP Membership Committee. He is Senator of the University of Alberta, member of the AAPS Steering Committee for In Vitro Release and Dissolution; Vice Chair of the Specialty Committee of Traditional Chinese Medicine in Pharmaceutics; World Foundation of Chinese Medicine Science

Ian MacLachlan
Tekmira Pharmaceuticals Corporation, Burnaby, BC

Dr. Ian MacLachlan is currently the Chief Scientific Officer and Executive Vice President of Tekmira Pharmaceuticals Corporation. He joined Tekmira in 2008 when Tekmira merged with Protiva Biotherapeutics. Dr. MacLachlan co-founded Protiva in 2000 and was Protiva's Chief Scientific Officer until 2008. Prior to Protiva, he was a research scientist at Inex Pharmaceuticals Corporation. He received his B.Sc. and Ph.D. in Biochemistry from the University of Alberta and spent two years at the Vienna Bio-Center researching systemic gene delivery. He conducted postdoctoral research at the Howard Hughes Medical Institute at the University of Michigan in the laboratory of Dr. Gary Nabel, a pioneer in the development of DNA-based therapeutics.

Dr. MacLachlan has been active in molecular therapeutics for over a decade with a specific focus on advancing nucleic acid drugs including small interfering RNA and enabling delivery technology. Dr. MacLachlan has been an invited speaker on nucleic acid delivery at the National Institutes of Health, the National Cancer Institute, numerous academic institutions and major scientific meetings dealing with molecular therapy. He is a member of the New York Academy of Sciences, the Oligonucleotide Therapeutics Society and the American Society of Gene Therapy.

Norbert Maurer
Drug Delivery/Formulation Division, Centre for Drug Research and Development, Vancouver, BC

Dr. Maurer is running the Drug Delivery/Formulation Division at the Centre for Drug Research and Development (CDRD) and manages a small portfolio of preclinical drug development projects in the area of cancer and infectious disease. Dr. Maurer has over 13 years of experience in the development of formulation and delivery technologies for conventional chemotherapeutic agents as well as RNA, DNA and peptide-based therapeutics in both academic and industry settings. Previously, as the Principal Scientist at iCell Therapeutics, a Vancouver-based pharmaceutical start-up, he set up the R&D

infrastructure, successfully raised funding for the early stage development of the company's lead product, a nanoemulsion-based anticancer drug and directed the research activities. As a senior scientist at Inex Pharmaceuticals (now Tekmira Pharmaceuticals), he headed the formulation group. He was actively involved in early and late stages of clinical product development supporting out-licensing of 3 liposomal anticancer drugs and managed the company's discovery research programs. Dr. Maurer has a PhD in Chemistry from the Karl-Franzens University Graz and completed a postdoctoral fellowship in the Liposome Research Unit of the Biochemistry Department at UBC. He authored 27 peer-reviewed papers, review articles and book chapters and is an inventor on 6 patents/patent applications that support the product pipeline of 3 biotech companies.

Lawrence Mayer
Celator Pharmaceuticals, Vancouver, BC, Canada

Lawrence Mayer, Ph.D., is Founder, President & Head of Research, Celator Pharmaceuticals. Dr. Mayer has played a lead role in the discovery and development of a number of drugs through Phase II clinical trials, three of which eventually achieved market approval. He held senior management positions at The Canadian Liposome Company and QLT Inc. before joining the BC Cancer Agency, where he established and directed the Health Canada accredited Investigational Drug Program. Celator was formed in 2000 as a spin-out of Dr. Mayer's laboratory at the BC Cancer Agency. Dr. Mayer has authored more than 200 scientific publications and has more than 35 patents awarded or pending. Dr. Mayer received his B.S. in both Chemistry and Biology (1978), summa cum laude, from Wartburg College and his Ph.D. in Biochemistry (1983) from the University of Minnesota.

Shawnmarie Mayrand-Chung
The Biomarkers Consortium, National Institutes of Health, Bethesda, Maryland, USA

Dr. Shawnmarie Mayrand-Chung is the NIH Director for The Biomarkers Consortium (http://www.biomarkersconsortium.org) and works in the Program on Public-Private Partnerships Program at the National Institutes of Health (NIH) in Bethesda, Maryland.

She earned a Ph.D. in Biochemistry (Immunology) from Dartmouth Medical School in 1988, where she studied retroviral immunology and related immune responses, and received her J.D. from New York Law School in 2003. Dr. Mayrand-Chung worked in the field of patent law from 1998 to 2006, and joined the Office of Science Policy Analysis and the Program on Public-Private Partnerships Program (http://ppp.od.nih.gov/) in 2007.

In her role as NIH Director for The Biomarkers Consortium, Dr. Mayrand-Chung works directly with the NIH Institute Directors and scientists on all aspects of the Consortium and works closely with the Foundation for NIH in her capacity of as Senior Advisor to The Biomarkers Consortium.

As a member of Public-Private Partnerships Program at the National Institutes of Health she is involved in all aspects of partnership development for the NIH.

Bruce McManus
Department of Pathology and Laboratory Medicine, University of British Columbia, Vancouver, BC, Canada

Bruce McManus is Professor, Department of Pathology and Laboratory Medicine, at the University of British Columbia. He serves as Director of the UBC James Hogg iCAPTURE Centre for Cardiovascular and Pulmonary Research and of the Providence Heart + Lung Institute at St. Paul's Hospital. Since 2008, Dr. McManus also directs the Centre of Excellence for the Prevention of Organ Failure (PROOF), one of the federally-funded, not-for-profit Centres of Excellence for Commercialization and Research (CECR). Dr. McManus served as the inaugural Scientific Director of the Institute of Circulatory and Respiratory Health, Canadian Institutes of Health Research, from December 2000 until April 2006. In this capacity, he led the development and implementation of a strategic research plan for Canada to address scientific questions related to cardiac, respiratory, vascular, brain (stroke), blood, sleep, and intensive care-related disorders and diseases. Dr. McManus received BA and MD degrees from the University of Saskatchewan, an MSc in Applied Physiology from Pennsylvania State University, and the PhD in Exercise Physiology and Biochemistry from the University of Toledo. He pursued post-doctoral training in Environmental Physiology at the University of California - Santa Barbara. Dr. McManus completed residency training at the Peter Bent Brigham Hospital-Harvard University in

Internal Medicine and Pathology, and in Cardiovascular and Pulmonary Pathology at the National Heart, Lung, and Blood Institute in Bethesda, MD. Following 11 years as a faculty member at the University of Nebraska Medical Centre, including a sabbatical as John F. Fogarty Senior International Fellow at the Max Planck Institute for Biochemistry, Martinsried, Germany, Dr. McManus joined the Faculty of Medicine of the University of British Columbia as Department Head of Pathology and Laboratory Medicine in July 1993, a post he held until December, 2000. Dr. McManus is a Fellow of the Royal College of Physicians and Surgeons of Canada, the College of American Pathologists, the American College of Cardiology and the American College of Chest Physicians. Dr. McManus' investigative program is focused on mechanisms, consequences, detection and prevention of injury and aberrant repair in inflammatory disease of the heart and blood vessels, with particular emphasis on enteroviral infections of the heart and allograft rejection. He works in an interdisciplinary setting enabled by colleagues in the health professions, the life sciences, engineering and computational sciences. In addition to basic science approaches, he is engaged in "-omic" biomarker discovery, development, commercialization and implementation. He also participates in development of user tools for data acquisition, annotation, and use. He has long been involved in registry development and biobanking to support heart and lung research. Dr. McManus has co-authored over 300 peer-reviewed publications and 50 chapters. He has edited four books including Transplant Pathology, Atlas of Cardiovascular Pathology for the Clinician (now 2nd edition), and Idiopathic Dilated Cardiomyopathy. He co-holds several patents for inventions. He has served as Councilor for the International Society for Heart Research and for the American Society for Investigative Pathology. He is past-president of the Society for Cardiovascular Pathology, and has served the Society as Councillor, Membership Chair, and Program Chair. Dr. McManus serves on the editorial board of several professional and scientific journals, and on many advisory committees and boards. He has long been committed to training and mentoring scientist and clinical trainees across a range of disciplines. He has shared his passion for scientific inquiry and pathology, generously giving of his time and never-ending energy in nurturing 7 postdoctoral fellows and 34 graduate students, as well as >50 undergraduate and pre-doctoral students and scores of pathology residents. He has provided short courses or special courses for the US & Canadian Academy of Pathology, International Society of Heart and Lung Transplantation, American College of Cardiology, and American Academy of Restorative Dentistry. He has convened many public and private sector partnerships in research, development and education. Dr. McManus has been recognized for his scientific contributions by numerous institutions through visiting professorships and lectureships. He was co-recipient of the prestigious Max Planck Research Award with Dr. Reinhard Kandolf in 1991. He was elected to the Royal Society of Canada as a Fellow of the Academy of Sciences in 2002. He received a UBC Killam Research Prize-Senior Scientist Category, and was elected as Fellow of the International Academy of Cardiovascular Sciences in 2003. In 2005, he was elected as an inaugural Fellow of the Canadian Academy of Health Sciences and was honoured with the Research Achievement Award of the Canadian Cardiovascular Society. In 2006 Dr. McManus received the BC Innovation Council's Lieutenant Governor's Technology Innovation Award. He has been honored with the 2007 UBC Distinguished Medical Lecturer Award and 2008 David F. Hardwick Lifetime Achievement Award. Dr. McManus was awarded the 2009 CSATVB Scientific Excellence Award of the Canadian Society for Atherosclerosis, Thrombosis and Vascular Biology, and recently, he was recognized as recipient of the 2010 Research & Mission Award from Providence Health Care and the 2010 Distinguished Achievement Award from the Society for Cardiovascular Pathology. Dr. McManus has had the pleasure of working professionally with his wife, Janet Wilson-McManus, for nearly three decades, and of watching the children, Alex, Amity and Cate, and grandson, Oscar, grow joyfully.

Scott McNeil
SAIC-Frederick Inc./NCI at Frederick, Frederick, MD, USA

Dr. Scott McNeil serves as Director, Nanotechnology Characterization Laboratory for the National Cancer Institute at Frederick where he coordinates pre-clinical characterization of nanomaterials intended for cancer therapeutics and diagnostics. He advises Industry and State and US Governments on the development of nanotechnology and is a member of several governmental and industrial working groups related to nanotechnology

policy, standardization and commercialization. Prior to joining NCI-Frederick (i.e. SAIC-Frederick), he served as Senior Scientist in the Nanotech Initiatives Division at SAIC where he transitioned basic nanotechnology research to government and commercial markets. Dr. McNeil's professional career includes tenure as an Army Officer, with tours as Chief of Biochemistry at Tripler Army Medical Center, as a Combat Arms officer in the Gulf War. He is an invited speaker to numerous nanotechnology-related conferences and has six patents pending related to nanotechnology and biotechnology. He received his bachelor's degree in chemistry from Portland State University and his doctorate in cell biology from Oregon Health Sciences University.

Bruce E. Miller
Discovery Medicine, Respiratory Centre of Excellence for Drug Discovery, GlaxoSmithKline, King of Prussia, PA, USA

Dr. Miller is currently a Director in Discovery Medicine in the Respiratory Centre of Excellence for Drug Discovery at GlaxoSmithKline. Dr. Miller received his Ph.D. in Toxicology & Pharmacology from the University of North Carolina at Chapel Hill and completed postdoctoral training at the National Institute of Environmental Health Sciences (NIH) and Glaxo Inc. He has over 20 years of experience in the pharmaceutical industry and has held various positions in the areas of Drug Discovery and Clinical Research. In his current role, Dr. Miller is responsible for designing translational studies to support the early clinical development (Phase I, First Time in Human Studies to Phase II, Proof Concept Patient Studies) of new compounds for the treatment of Chronic Obstructive Pulmonary Disease (COPD). Current research activities focus on the identification and characterization of biomarkers that can be used as intermediates to support new drug development for COPD. Dr. Miller is a co-leader of the ECLIPSE (Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints) Biomarker Team and a member of the ECLIPSE Scientific Committee.

Marnie Mitchell
British Columbia Pharmacy Association, Vancouver, BC, Canada

Ms. Marnie Mitchell assumed the position of CEO for the British Columbia Pharmacy Association (BCPhA) in June 2003. In her role with BCPhA, she is accountable for the management and direction of the professional advocacy association representing over 2,000 pharmacists and 650 pharmacies. Specific accomplishments have been growth of membership since 2003; support for expanded pharmacist scope of practice including the adapting prescriptions and injections roles which took effect in 2009; negotiation of an Interim Agreement with the Ministry of Health in 2008; completion of the Activity Based Costing study of pharmacy services in B.C.; and support for clinical services practice proposals.

She held the position of Executive Director with PharmaCare, Ministry of Health in Victoria BC between 1999 and 2003. In her role with PharmaCare, she was responsible for all aspects of policy and program management including development and maintenance of stakeholder relations; initiation of Fair PharmaCare program and initiation of the Common Drug Review. Previously, she held the role of Executive Director with the Public Sector Employers' Council Secretariat, also in Victoria, where she was involved with the start up in 1993 and subsequently worked with the crown corporations, colleges and universities sectors. Prior to these two roles she worked as a self-employed consultant and held a number of positions with the Ministry of Labour in Victoria.

Ms. Mitchell received her B.A. (with distinction), majoring in political science / history, and her M.A. in International Affairs, both from Carlton University in Ottawa. She has also studied towards her Ph.D. in Political Science at Dalhousie University in Halifax.

Leza Muir
Pacific Blue Cross, Vancouver, BC, Canada

Leza Muir is responsible for all Health and Dental claims functions for Pacific Blue Cross, including Office Services and Facilities.
Leza has been with Pacific Blue Cross for over 30 years and has had many roles in various departments. Her current responsibilities include researching and implementing various business and technological strategies/projects that complement and enhance the core business functions.
Leza represents Pacific Blue Cross on various committees including the Canadian Blue Cross National Benefits & Management Claims Committee, the National Electronic Claims Standards Executive Steering Committee and has

participated on a number of British Columbia Working Groups such as the Chronic Disease Management (CDM/QI) Task Force. Leza has also served on a number of advisory Committees for the pharmaceutical industry.
Leza is also a director of the Burnaby Board of Trade and a director for Burnaby Family Life. Leza is a member of the Burnaby Board of Trade's Executive Committee and is Chair of the Governance Committee, and a member of the Burnaby Family Life's Continuous Quality Improvement Committee as well as the Nominating Committee.

Russell J. Mumper
Eshelman School of Pharmacy, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

Dr. Mumper is the first Director of the Center for Nanotechnology in Drug Delivery at The University of North Carolina at Chapel Hill. Dr. Mumper's research program focuses on nano-based delivery systems for cancer and vaccines, drug-polymer conjugates, and (trans)mucosal drug and vaccine delivery.
From 1999-2007, Dr. Mumper was a faculty member in the Department of Pharmaceutical Sciences in the College of Pharmacy at the University of Kentucky (UK).
Dr. Mumper was also the Associate Director of the Center for Pharmaceutical Science & Technology (CPST), a unique university-based fully-integrated FDA-registered GMP pharmaceutical manufacturing facility. From 1992-1999, Dr. Mumper held various product development positions in the pharmaceutical/biotech industry. Since returning to academia in 1999, Dr. Mumper has received over $14 million in research grants/contracts comprising 30 grants/contracts from Federal or Foundation sources and 50 from Industry. Dr. Mumper has more than 205 scientific publications/abstracts and 38 patents or patents pending. In 2006, he received the AAPS Lipid-based Drug Delivery Award sponsored by Gattefossé Corporation. In 2007, he received a "Great Teacher" award sponsored by the UK Alumni Association. Dr. Mumper has co-founded four companies based on technologies developed in his laboratories. In 2009, Dr. Mumper was elected as a Fellow of the AAPS. Dr. Mumper received a B.A. in Chemistry and Ph.D. in Pharmaceutics/Drug Delivery from the University of Kentucky in 1988 and 1991, respectively.

Reza Oliyai
Formulation and Process Development, Gilead Sciences, Foster City, CA, USA

Dr. Oliyai is the Senior Director of Formulation and Process Development at Gilead Sciences. He received his B.S. degree in Pharmacy from Oregon State University in 1988. He then received his M.S. (1990) and Ph.D. (1993) degrees in Pharmaceutical Chemistry from the University of Kansas. Dr. Oliyai joined Gilead in 1994 and he is currently responsible for discovery pharmaceutics and lead optimization, preformulation, formulation development, and process scale-up of all the pre-clinical and clinical drug candidates. In addition, he serves as a Corporate Project Team Leader coordinating multidisciplinary functions including Clinical, Regulatory, Research, Pharmaceutical Development, and Commercial Strategy. Dr. Oliyai is a co-inventor of Viread®, Truvada™, and Atripla®. He has been involved in the development of a number of Gilead's other products including Tamiflu®, Hepsera®, and Letairis®. Dr. Oliyai is an author of over 30 scientific publications in peer-reviewed journals in the areas of oral prodrug design, chemical stability, formulation development, and pharmacokinetics. He is an inventor on multiple U.S. and international patents.

Michael F. Pintek
Luminex Corporation, Austin, TX, USA

Mr. Pintek joined Luminex Corporation as Senior Vice President of Operations in July of 2009. He joined Luminex from Roche, where he held several positions of increasing responsibility since 2001, most recently as Vice President and General Manager, Blood Screening, Roche Molecular Systems. Prior to Roche, his experience includes positions with Ventana Medical Systems and Abbott Laboratories' Diagnostics Division. Mr. Pintek holds a B.S. in Business Administration from Central Michigan University.

Micheline Piquette-Miller
Faculties of Pharmacy and Medicine, University of Toronto, Toronto, ON, Canada

Dr. Micheline Piquette-Miller's research specializes in the area of drug transport and molecular pharmacokinetics. Dr. Piquette-Miller completed a pharmacy degree and PhD in Pharmacokinetics at the University of Alberta and continued post-

doctoral training at the University of California in San Francisco. She is currently a Professor at the University of Toronto within the Faculties of Pharmacy and Medicine. Dr. Piquette-Miller has been the recipient of numerous prestigious national and international research awards and has held positions on the executive councils of the *American Society of Clinical Pharmacology and Therapeutics,* the *Canadian Society of Clinical Pharmacology* and the *Canadian Society of Pharmaceutical Science*. She is currently past-president of the *Canadian Society of Pharmacology and Therapeutics* and is an Associate Editor of Nature's *Clinical Pharmacology and Therapeutics.*

Christopher J.H. Porter
Monash Institute of Pharmaceutical Sciences, Monash University, Parkville, Melbourne, Australia

Chris Porter is Professor of Pharmaceutics at the Monash Institute of Pharmaceutical Sciences and Associate Dean (Research) of the Faculty of Pharmacy and Pharmaceutical Sciences at Monash University, Melbourne. He completed his undergraduate and graduate studies at the University of Nottingham in the UK before moving to Australia and Monash in 1992. Subsequently, Chris' research program has focused on understanding and quantifying drug absorption, distribution and elimination profiles and on developing the models and techniques to probe these interactions. A major interest has been the issues and problems surrounding the absorption of poorly water soluble, highly lipophilic drugs and in particular the use of lipid based delivery systems and microemulsions to enhance oral bioavailability and stimulate lymphatic transport. More recently, his interests have expanded into the mechanisms of cellular transport of lipophilic drugs and the potential utility of dendrimers as drug delivery systems. Chris has published more than 100 peer reviewed papers in these areas and has trained more than 30 PhDs and post doctoral fellows. Chris received the American Association of Pharmaceutical Scientists (AAPS) Lipid Based Drug Delivery Outstanding Research Award in 2009 and New Investigator Award in 1999. He was also the recipient of the Victorian College of Pharmacy Deans award for Education (2005) and Research (2007). He is a current member of the Editorial Boards of Pharmaceutical Research, the Journal of Pharmaceutical Sciences and the Journal of Pharmacy and Pharmacology and is a Fellow of the Royal Australian Chemical Society.

Graham Robertson
Cancer Pharmacology Unit, ANZAC Research Institute, Concord Hospital, and University of Sydney, Sydney, Australia

A/Prof Robertson is a research scientist within the University of Sydney and a Senior Research Fellow of the ANZAC Research Institute at Concord RG Hospital, NSW Australia. He is the senior scientist and group leader responsible for establishing the Cancer Pharmacology Unit and coordinating the pre-clinical research program as well as a Cancer Institute NSW translational program grant to use advanced proteomic techniques to discover protein biomarkers for colorectal cancer.

Graham's research interests are: mechanisms of hepatic gene regulation; impact of tumour-derived cytokines on drug disposition and the development of cancer cachexia; regulation of metabolic pathways by nuclear receptors; development of transgenic mouse models for liver studies; pathophysiology of liver injury; discovery of biomarkers for cancer.

Alan B Sachs
Merck Research Laboratories, Sirna Therapeutics/ Merck & CO Inc., San Francisco, CA, USA

Dr. Alan Sachs, Vice President, Merck Research Laboratories (MRL), assumed responsibility for Merck's high throughput screening, structural biology, and sample collection in 2009. He assumed leadership of Sirna Therapeutics and established the global MRL RNA Therapeutics Department effective January 4, 2007. Prior to this, Dr. Sachs assumed responsibility for the scientific leadership at Rosetta Inpharmatics LLC effective July 2002, responsibility for the Rosetta site effective March, 2004, and overall responsibility for the Department of Molecular Profiling in 2006. Dr. Sachs joined Merck & Co., Inc. as Director of Clinical Genomics for MRL in July 2001.

Prior to joining Merck, Dr. Sachs was Associate Professor of Molecular and Cell Biology while at the University of California at Berkeley, and a Whitehead Institute Fellow at the Whitehead Institute in Cambridge. Dr. Sachs is one of the leading figures in the field of mRNA translation and regulation, and has made landmark contributions, particularly to the understanding of the role of the poly(A) tail in translation and mRNA stability.
Dr. Sachs graduated from Cornell University with a B.A. in Biochemistry; received his Ph.D. in Cell

Biology at Stanford University; his M.D. from Stanford Medical School; and completed a post-doctoral fellowship in the Department of Biochemistry, Stanford University.

Suzanne C. Malfair Taylor
Pharmaceutical Services Division, BC Ministry of Health Services, Vancouver, BC

Suzanne Malfair Taylor is a Doctor of Pharmacy with Board Certification in Pharmacotherapy, who did her BSc in Pharmacy and her PharmD at UBC. She also completed a hospital pharmacy residency at Vancouver General Hospital; a BCIT Healthcare Management certificate; and several pharmacoeconomics and outcomes research programs. She spent 12 years at the BC Cancer Agency working in clinical, educational, and research capacities. Currently, she is Executive Director of the Drug Use Optimization Branch within the Pharmaceutical Services Division at the BC Ministry of Health Services as well as a Clinical Professor with the UBC Faculty of Pharmaceutical Sciences. Her branch at the Ministry helps educate the province about the appropriate use of medications to achieve improved health outcomes in a fiscally responsible manner. She has a special interest in Real World Safety and Effectiveness and real world cost-effectiveness. Other than drugs, she enjoys curling, aerobics, boating, and spending as much time as possible with her husband Cliff and her 2 young daughters (Jensen 7.5yrs and Chelsea 5.5yrs).

Xiaowei (Shirley) Teng
BRI Biopharmaceutical Research Inc. Vancouver, BC, Canada

Dr. Xiaowei Teng is a Research Scientist at BRI who has broad and in-depth experience in bioanalytical, DMPK/Tox. She graduated with a Bachelor's degree in Pharmacy from China and a Ph.D. in Pharmaceutical Sciences from The University of Sydney, Australia in 2002. After her undergraduate study, she became a clinical pharmacist working on therapeutic drug monitoring in China where she began her experience in analytical method development and clinical pharmacokinetics. Since her graduate study in Australia, and her post-doctoral training in Washington State University, USA, and in University of British Columbia, Canada, she has further explored her experience in drug metabolism, pharmacokinetics and drug induced hepatotoxicity. She joined BRI in 2007 and served as a research scientist and team leader, managing projects in bioanalytical assay development, *in vitro* and *in vivo* DMPK in a GLP environment. She is highly experienced in bioanalytical assay development using LC/MS/MS, LC/MS, GC/MS and other instrumental analysis, cytochrome P450 profiling, P450 inhibition and induction, metabolite identification, and *in vivo* pharmacokinetics. She has contributed to over 20 scientific publications in peer-reviewed scientific journals.

Nageshwar R. Thudi
Ranbaxy Pharmaceuticals, Mississauga, ON, Canada

Dr. Thudi has over 12 years of experience in CRO and generic pharma industry. He is currently working as group leader at Ranbaxy Pharmaceuticals in the department of clinical pharmacology and pharmacokinetics. At Ranbaxy he is responsible for protocols design, pharmacokinetics and monitoring for global submissions. He has 18 publications in peer reviewed journals on and one book chapter on bioanalysis. He currently associated with SOCRA and member of generic BE committee of CGPA.

Anne Tomalin
CanReg Inc., Dundas, ON

Anne Tomalin, B.A., B.Sc., RAC (U.S. & EU), President of CanReg Inc., has practiced exclusively in the area of regulatory affairs in Canada since 1971. Over that time, she has worked with three international pharmaceutical companies to obtain registrations for prescription pharmaceuticals, OTCs and medical devices. Anne founded CanReg Inc., a regulatory affairs consulting company, in September 1996. Ten years later, CanReg has 110 full time employees, and is one of the most successful regulatory consulting firms in Canada.

Prior to founding CanReg, Anne was employed for 20 years with Searle Canada, A Unit of Monsanto Canada Inc., as a Business Unit Director. Responsibilities in the last several years at Searle included regulatory affairs, provincial government, reimbursement strategies, managed care, customer interface, legal and information services. Prior to joining Searle, Anne was employed by Hoffmann-LaRoche Limited for three years, and prior to Roche, Anne was employed by Wyeth Ltd. Anne is a graduate of York University, and holds a B.A. degree in English and a B.Sc. Degree in Chemistry.

Mark A. Tracy
Pharmaceutical Operations, Alnylam, Inc., Boston, MA, USA

Dr. Tracy is Senior Director of Pharmaceutical Operations at Alnylam, Inc. He leads development activities in translating siRNA formulations from research to the clinic and is responsible for pharmaceutics, drug delivery, and delivery technology assessment. Most recently, he played a key role in advancing a novel systemically delivered lipid-based siRNA formulation to an IND filing, the first dual targeting RNAi therapeutic to advance to this stage of development. Previously, Dr. Tracy was Director of Formulation Development at Alkermes, Inc. where he and his group were responsible for the development of inhaled and injectable formulations of biologics and small molecules. He was a member of the team that developed and scaled-up the first sustained delivery system for proteins approved by the FDA and commercialized and contributed to the development of Risperdal® Consta and Vivitrol®, two small molecule containing microsphere sustained release formulations on the market. Dr. Tracy also contributed to the development of new inhalation technologies. He led project teams and various collaborations from feasibility through clinical testing. Dr. Tracy received his Ph.D. in Chemistry from Stanford University. He holds an M.S. in Chemical Engineering from Stanford and a B.S. summa cum laude in Chemical Engineering from the University of Illinois. Dr. Tracy has published journal articles and patents in the areas of drug delivery, pharmaceutics, polymers and colloids, and proteins and peptides. He is an adjunct associate professor in the Department of Pharmaceutical Sciences at Northeastern University and a lecturer at Brown University, and previously Harvard and the Massachusetts College of Pharmacy. He is President-elect of the Controlled Release Society (CRS) in 2009-10 and previously served on the CRS Board of Scientific Advisors. He is a Fellow of AIMBE. He is a member of AIChE, ACS, AAPS, PDA, and AAAS.

Mervyn J. Turner
Merck & Co., Inc., and Emerging Markets, Merck Research Laboratories, Rahway, NJ, USA

Dr. Mervyn Turner joined Merck Research Laboratories in 1985. Over the last 25 years, he has held many positions of increasing responsibility at Merck. In August 1999, Dr. Turner was appointed Senior Vice President, Merck Frosst Centre for Therapeutic Research in Montreal, Canada. Dr. Turner returned from his assignment in Montreal in October 2002 to take up the position of Senior Vice President, Worldwide Licensing and External Research. In this role, he was responsible for the oversight of all of Merck's licensing activities, and for the management of academic relations. Through his multiple and diverse experiences in the Merck Research Laboratories, Dr. Turner has acquired a broad perspective on the issues surrounding drug discovery and development.

2004 through 2008 saw a sizeable increase in deal activity for Merck, with over 190 transactions completed. Merck has also been active in M&A, with Aton, Abmaxis, GlycoFi, Sirna and NovaCardia, all acquired to build areas of key strategic importance. Dr. Turner saw all this activity as a logical product of a cultural shift within Merck towards a more outward-facing organization.

In September 2008, Dr. Turner was also appointed to the newly created role of Chief Strategy Officer for Merck & Co. Inc. where he leads the formulation and execution of Merck's long term strategic plan and the linkage of that strategy to the business plans of Merck's Franchises, Divisions, and Functions. In November 2009, Dr. Turner turned over the licensing reins when, in addition to his CSO role, he was appointed Senior Vice President, Emerging Markets, Merck Research Laboratories where he is responsible for developing MRL strategy to both support our commercial aspirations in the regions, and also to leverage emergent capabilities in India and China to the global benefit of the MRL pipeline.

Dr. Turner is the author of over 80 articles in peer reviewed journals. He has served on the Editorial Board of a number of journals, and from 1998 to 2008 he was a member of Health Care Ventures Scientific Advisory Board.

Elizabeth B. Vadas
InSciTech Inc., Dorval, Quebec

Elizabeth B. Vadas received her Ph.D. in Physical Chemistry from McGill University in Montreal. She obtained her undergraduate degree in colloid and surface chemistry in Budapest, Hungary. She joined Merck Frosst, the Canadian subsidiary of Merck & Co. in 1980 as a senior research scientist in the department of Pharmaceutical Research and Development. Over the years she has been involved

in the formulation development of many new chemical entities discovered at the Merck Frosst Centre for Therapeutic Research while taking on increasing management responsibilities.

From 1991 to 2002 Dr. Vadas was head of Pharmaceutical Research and Development at Merck Frosst The department, under her leadership, was responsible from early compound characterization to formulation and process development of new chemical entities including the supply of clinical trial materials from phase I through phase III and technical transfer to manufacturing. Notable accomplishments of her department were several products developed for worldwide introduction. One of the most important of these products from the leukotriene program, leading to worldwide regulatory approval, was SINGULAIR®, Merck's once a day oral asthma therapy

In mid-2002 Dr. Vadas decided to take early retirement to establish her own consulting company, InSciTech Inc. Currently she works with several drug discovery companies in the US, Canada and in Europe, providing development expertise.

Dr. Vadas has lectured and published widely. She is a Fellow of AAPS, Past President of the Canadian Society for Pharmaceutical Sciences and has been an adjunct professor of pharmaceutics at the University of Montreal for several years. She is the recipient of a number of scientific and management awards.

Kishor M. Wasan
Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, BC, Canada

Dr. Kishor M. Wasan (www.wasanlab.ubc.ca) is a Distinguished University Scholar Professor at the University of British Columbia in Vancouver, BC, Canada. In the 15 years that Dr. Wasan has been an independent researcher at UBC, he has published over 180 peer-reviewed articles and 220 abstracts in the area of lipid-based drug delivery and lipoprotein-drug interactions. His work was recently highlighted in the January 2008 Issue of Nature Reviews, Drug Discovery.

Dr. Wasan was one of the recipients of the 1993 American Association of Pharmaceutical Scientists (AAPS) Graduate Student Awards for Excellence in Graduate Research in Drug Delivery, the 2001 AAPS New Investigator Award/Grant in Pharmaceutics and Pharmaceutics Technologies, the 2002 Association of Faculties of Pharmacy of Canada New Investigator Research Award and recently was named an AAPS fellow in 2006. In addition, Dr. Wasan was awarded a Canadian Institutes of Health Research University-Industry Research Chair in Pharmaceutical Development (2003-2008), was named a University Distinguished Scholar in April 2004 received the 2007 AAPS Award for Outstanding Research in Lipid-Based Drug Delivery and the 2008 AFPC-Pfizer Research Career Award. In April 2009 Dr. Wasan was named CIHR/iCo Therapeutics Research Chair in Drug Delivery for Neglected Global Diseases. Currently Dr. Wasan's research is supported by several grants from The Canadian Institutes of Health Research, several pharmaceutical companies and the National Cancer Institute of Canada-Clinical Trials Group. In addition, Dr. Wasan is one of the founding members of the University of British Columbia's Neglected Global Diseases Initiative (www.ngdi-ubc.com). To date the initiative has raised over 1.2 million dollars towards on new therapeutics for neglected diseases.

Wen Xie
Pharmaceutical Sciences and Pharmacology, and Center for Pharmacogenetics, University of Pittsburgh, Pittsburgh, PA, USA

Dr. Wen Xie is Associate Professor of Pharmaceutical Sciences and Pharmacology, and Associate Director of Center for Pharmacogenetics, University of Pittsburgh. Dr. Xie's laboratory studies orphan nuclear receptor-mediated regulation of genes encoding drug metabolizing enzymes and transporters. The same enzymes and transporters are also responsible for the homeostasis of endobiotics that include steroid hormones, cholesterol, lipids, bile acids and bilirubin. Research in Xie lab has helped to establish members of the orphan nuclear receptors, such as PXR, CAR, LXR, and ROR, as xeno- and endo-sensors that sense xeno- and endobiotics which, in turn, lead to enzyme and transporter gene regulation. This regulation has broad implications in drug metabolism and drug development. Moreover, these orphan receptors can be explored as therapeutic targets for the treatment and prevention of human diseases, such as cholestasis, jaundice, gallstone disease, breast cancer, prostate cancer, and colon cancer.

To better understand the transcriptional regulation of enzymes and transporters and the significance of this regulation *in vivo*, Xie lab has created a wide array of genetic engineered mice with compromised (gene knockout), heightened (transgenic), or humanized receptor activities. The

humanized mice, created by replacing the mouse receptor with its human counterpart, have provided unique tools to dissect the orphan nuclear receptor-mediated gene regulation through molecular, genomic, and pharmacological approaches.

Research in Xie lab has been funded by grants from US National Institutes of Health's National Institute of Environmental Health Sciences (NIEHS), National Cancer Institute (NCI), National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK).

Dr. Xie has authored or co-authored ~90 peer reviewed papers and book chapters. He is the sole Editor for the Wiley book "Nuclear Receptors in Drug Metabolism" published in 2009. Among his other achievements, Dr. Xie is the recipient of 2008 University of Pittsburgh Chancellor's Distinguished Research Award, 2008 James R. Gillette ISSX North American New Investigator Award, and 2009 American Society for Pharmacology and Experimental Therapeutics (ASPET) Division for Drug Metabolism Early Career Achievement Award.

Robert Young
Department of Chemistry, Simon Fraser University, Burnaby, BC, Canada

Dr. Robert Young earned a B.Sc. (1967) from the University of Victoria, a Ph.D. (1971) from the University of British Columbia, and continued postdoctoral studies at the Imperial College of Science and Technology, the University of Adelaide and the University of British Columbia between 1971 and 1976. From 1976 to 1977, he was a Research Associate at the Institut de Chimie des Substances Naturelles in Gif-sur-Yvette, France, and from 1977 until 2006 he worked in various capacities with Merck Frosst Canada & Co. He was Vice-President and Head of Medicinal Chemistry at the Merck Frosst Centre for Therapeutic Research before taking early retirement in 2006. He is now Professor of Chemistry and Merck Frosst-B.C. Leadership Chair in Pharmaceutical Genomics, Bioinformatics and Drug Discovery in the Chemistry Department at Simon Fraser University. His current research is focused on the design and use of novel pharmacological probes and proof of concept molecules for the discovery and validation of new drug targets. He is also director of the Division of Medicinal Chemstry of the Center for Drug Research and Development (CDRD) in British Columbia and consults for a number of Pharmaceutical companies through his own company, Promorpheus Consultants Inc.

Dr. Young's career has focused on the design and synthesis of novel drugs for asthma, inflammation, osteoporosis and related diseases and he is most noted for his part in the discovery of the asthma drug, Singulair™. Dr. Young is the author of more than 160 publications, review articles and patents.

Dr. Young is a member of the Order of Canada and a Fellow of the Royal Society of Canada, and his academic and professional honours and affiliations are numerous. He was awarded a National Merit Award from the Ottawa Life Sciences Council and a Heroes of Chemistry Award from the American Chemical Society. He was appointed a member of the Natural Sciences and Engineering Research Council of Canada and was recently recipient of the Award of Leadership in Pharmaceutical Sciences from the Canadian Society for Pharmaceutical Sciences and the first Genome BC Leadership Award.

Hong Zhao
Organic & Medicinal Chemistry, Enzon Pharmaceuticals, Inc., Piscataway, NJ, USA

Dr. Hong Zhao (Ph.D. Organic Chemistry, Rutgers – the State University of New Jersey) is the Director of Organic & Medicinal Chemistry Department at Enzon Pharmaceuticals. He joined Enzon in 1997. At Enzon, Dr. Zhao is responsible for Customized PEG Linker technology development and new drug delivery research.

His research interests focus on the development of novel drug delivery techniques, including polymeric drug conjugates and novel nanoparticle formulations. Dr. Zhao has received the Inventors Award (1998-2009) and Best Publication Award (2003, 2004) in recognition of his accomplishments at Enozn. He is also the author of 31 publications and 54 patents and patent applications.

CSPS
Poster Presentations
Day 1
Thursday, June 3, 2010

Day 1

Biomedical Sciences

1. Effects of Docosahexaenoic Acid in Ischemia-Reperfusion Injury

Rawabi S Qadhi[1], Shahir Mishriki[1], Sri Nagarjun Batchu[1], Ketul R Chaudhary[1], John M Seubert[1]. [1]Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, CA

Purpose: Cardiovascular disease (CVD) remains a major cause of illness, disability and death worldwide. Ischemia reperfusion (IR) injury results from damage incurred after severe impairment of the arteries that feed the heart muscle when both blood flow and oxygen supply are restricted. The importance of dietary polyunsaturated fatty acids (PUFA) in the reduction of cardiovascular disease has been recognized for many years; yet their protective role toward IR injury and mechanism(s) of action remain unknown. Ecosapentaenoic acid (20:5n3, EPA) and docosahexaenoic acid (22:6n3, DHA) are two of the most important n-3 PUFA. As these are not synthesized in the human body they are obtained from dietary sources, such as fish oil. The objective of this study was to investigate the protective effects of DHA in acute IR injury.
Methods: Hearts from C57BL6 mice were isolated and perfused in Langendorff mode for 40min of baseline and subjected to 30min of global no-flow ischemia followed by 40 min of reperfusion and functional recovery was monitored. Dose-response effects were determined in hearts perfused with DHA (10μM, 50μM or 100μM). Rat myoblast cells (H9c2 cells) were subjected to 6 or 24 hours hypoxia followed by 16 hours reoxygenation. Cell viability (Trypan blue and MTT assays), cellular reactive oxygen species (ROS) and caspase-3 activities were then measured to compare cellular injury in DHA treated cells versus control.
Results: Perfusion with DHA resulted in decreased postischemic left ventricular developed pressure (LVDP) recovery in hearts treated with DHA (31.2±14.8% N=5, 20.1±10.3% N=4 and 36.4±14.7% N=4 at 10μM, 50μM and 100μM, respectively). DHA increased ROS production suggesting that DHA cause oxidative stress in H9c2 cells. DHA trigger cell proliferation under normoxic conditions.
Conclusion: Our data suggests that acute treatment of DHA is detrimental to ischemia-reperfusion injury.

2. A Novel Anti-angiogenesis Mechanism of Angiostatin: Inhibition of Endothelial Cell MMP-2 Production

Corey Ramer and Paul Jurasz. Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, Alberta, Canada.

Purpose: Angiostatin is an endogenous angiogenesis inhibitor which limits collateral vessel growth in coronary artery disease patients. Currently, controversy exists whether angiostatin inhibits endothelial cell (EC) migration and/or induces apoptosis. Experimental evidence suggests an acidotic extracellular environment promotes angiostatin-induced EC apoptosis. Ischemic tissues become acidotic as a consequence of hypoxia. However, hypoxia stimulates EC expression of vascular endothelial growth factor (VEGF) which promotes EC survival. Angiostatin-induced EC apoptosis has been shown to be p53-dependent; however, p53 also inhibits matrix metalloproteinase-2 (MMP-2) expression, a molecular mediator of EC migration. Since hypoxia results in VEGF up-regulation, we hypothesized that under hypoxic conditions angiostatin's main mechanism of action may be inhibition of EC MMP-2 production and migration, and not apoptosis induction.
Methods: Cultured human microvascular endothelial cells (HMVEC) were exposed to either normoxic or hypoxic conditions for 48 hours in the presence/absence of angiostatin. Hypoxia was replicated in a Billups-Rothenberg chamber continually perfused with 5% CO_2, balance N_2. Apoptosis was assessed by flow cytometry. HMVEC MMP-2 and VEGF generation was measured using gelatin zymography and ELISA, respectively. HMVEC migration was studied using a modified Boyden Chamber assay.
Results: Angiostatin (30 □g/ml) did not significantly increase HMVEC apoptosis under normoxic (40.4±3.1 vs. 40.5±2.9%, $P > 0.05$) or hypoxic conditions (24.4±3.6 vs 28.8±4.1%, $P > 0.05$) despite a significant decrease in pH_e. This

result was likely due to VEGF up-regulation by HMVEC from undetectable levels under normoxic conditions to over 120 pg/ml during hypoxia. However, compared to control angiostatin only significantly decreased MMP-2 levels in HMVEC exposed to hypoxia (4098±500 vs 2640±157 arbitrary units of density/mg protein, $P < 0.05$). MMP-dependent migration of ECs was inhibited by angiostatin under hypoxic, but not normoxic, conditions.
Conclusion: Under hypoxic conditions angiostatin's primary anti-angiogenic mechanism is likely inhibition of endothelial cell MMP-dependent EC migration and not apoptosis induction.

3. Amphotericin B Concentrations in Target Organs of a Mouse Model of Visceral Leishmaniasis Following Successful Treatment Course by an Oral Lipid-based Formulation: Correlation to the Effect

Pavel Gershkovich[1], Xiaohua Zhu[2], Karl A. Werbovetz[2], Ellen K. Wasan[1,3], Olena Sivak[1], Richard R. Tidwell[4], John G. Clement[5], and Kishor M. Wasan[1]. [1]Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, Canada; [2]Division of Medicinal Chemistry and Pharmacognosy, College of Pharmacy, The Ohio State University, Columbus, Ohio; [3]School of Health Sciences, British Columbia Institute of Technology, Burnaby, BC Canada; [4]Department of Pathology and Laboratory Medicine, Consortium for Parasitic Drug Development, University of North Carolina at Chapel Hill, Chapel Hill, NC; [5]iCo Therapeutics Inc., Vancouver, Canada.

Purpose: To assess the concentration of amphotericin B (AmB) in liver and spleen of a mouse model of Visceral Leishmaniasis following successful treatment course by oral mono/diglyceride and phospholipid – based formulation of AmB (iCo-009).
Methods: Female Balb/c mice were infected by intravenous injection of *Leishmania donovani* promastigotes. The 5 day treatment course began one week post infection and included the following groups (n=5 each group): oral AmB formulation 20mg/kg BID and 10mg/kg BID, and IV Ambisome® 2mg/kg control group (one dose). The mice were sacrificed 72 hours following the completion of the treatment course, liver and spleen tissues were harvested and the concentrations of AmB were determined by HPLC. The obtained concentrations were correlated with previously reported effect on liver parasitemia.
Results: 72 hours following the completion of treatment course the concentrations of AmB in the liver were: 171 ± 15 ng/g for oral AmB 20mg/kg BID; 126 ± 27 ng/g for oral AmB 10mg/kg BID; and 263 ± 71 ng/g for IV Ambisome® 2mg/kg (one dose). The concentrations of AmB in spleen were as follows: 428 ± 82 ng/g for oral AmB 20mg/kg BID; 233 ± 61 ng/g for oral AmB 10mg/kg BID; and 6787 ± 836 ng/g for IV Ambisome® 2mg/kg (one dose). A good correlation was found between the measured concentrations of AmB in the liver and the observed effect on liver parasitemia.
Conclusions: Multiple dose treatment course of oral formulation of AmB (iCo-009) resulted in significant retention of AmB in target tissues (liver and spleen) in a mouse model of Visceral Leishmaniasis and considerable AmB concentrations were detected as late as 72 hours following the completion of the treatment. Higher concentrations of AmB were found in spleen relative to the liver in all treatment groups. The previously reported effect of eradication of *Leishmania donovani* amastigotes from the liver correlates directly to the actual AmB concentrations in liver tissue found in this study.
Acknowledgements: Funding for this Project was provided by CIHR, iCo Therapuetics Inc. and the Consortium for Parasitic Drug Development. This work was previously presented at the 2009 AAPS Annual Meeting in Los Angles CA, USA.

4. Protonated Nanoscale Aluminosilicate (NSAS) Reduces Plasma Cholesterol Concentrations and Atherosclerotic Lesion Formation in Apolipoprotein E(ApoE)-Deficient Mice

Kishor M. Wasan, Olena Sivak, Jerry Darlington, Pavel Gershkovich, Panayiotis P. Constantinides. University of British Columbia and AMCOL International, Vancouver, BC

Purpose: The aim of this work was to assess the effect of protonated nanostructured aluminosilicate (NSAS) on the plasma lipids levels and development of atherosclerotic lesions following chronic administration to ApoE-deficient mice.
Methods: Apolipoprotein E (ApoE) deficient mice were divided into the following treatment groups: protonated NSAS 0.11% w/w, 0.6% w/w, 1.4% w/w, untreated control and 2% w/w stigmastanol mixed with high-fat/high cholesterol diet. All animals were

treated for 12 weeks, blood samples were withdrawn every 4 weeks for determination of total plasma cholesterol and triglyceride levels. At the end of the study the animals were sacrificed and aortic root was harvested for histopathology assessment of atherosclerotic lesions.

Results: The 1.4% w/w NSAS treatment group showed statistically significant decrease (29%; from 986.3 ± 99.5 mg/dl in controls to 700 ± 42.4 mg/dl in 1.4% w/w NSAS treatment group; n=8, $p<0.05$) plasma total cholesterol levels at the end of the study (week 12) but not at earlier time points. The positive control (2% w/w stigmastanol) showed statistically significant decreases in plasma total cholesterol concentrations at all time points: 49.8% at week 12 (from 986.3 ± 99.5 mg/dl for controls to 495.5 ± 35.7 mg/dl for 2% stigmastanol group); 54.5% at week 8 (from 834.4 ± 36.8 mg/dl for controls to 379.8 ± 37.8 mg/dl for 2% stigmastanol group), and 59.9% at week 4 (from 723.2 ± 42.2 mg/dl for controls to 290.4 ± 28.3 mg/dl for 2% stigmastanol group). All other treatment groups have not shown statistically significant differences in plasma cholesterol concentrations relatively to the control group. The relative lesion sum area in NSAS 1.4% w/w treatment group was statistically significantly reduction (56%) from the control animals. The 2% w/w stigmastanol group showed statistically significant difference (58.8%) in total lesion area.

Conclusion: Chronic administration of protonated NSAS material resulted in a reduction of plasma cholesterol levels and decrease in development of atherosclerotic lesions within Apo-E deficient mice model.

Acknowledgements: Funding provided by AMCOL Int. This work was previous presented at the 2009 AAPS Annual Meeting in LA, CA.

5. *Ex vivo* Studies Suggest Doxorubicin and Daunorubicin are More Toxic than their Major Metabolites, Doxorubicinol and Daunorubicinol

Onkar S. Bains, Andras Szeitz, Joanna M. Lubieniecka, Thomas A. Grigliatti, Ronald E. Reid, and K. Wayne Riggs. Division of Pharmaceutics and Biopharmaceutics, Faculty of Pharmaceutical Sciences, The University of British Columbia, Vancouver, British Columbia, Canada (O.S.B., A.S., J.M.L., K.W.R.); Life Sciences Institute, Department of Zoology, Faculty of Science, The University of British Columbia, Vancouver, British Columbia, Canada (T.A.G.); Division of Biomolecular and Pharmaceutical Chemistry, Faculty of Pharmaceutical Sciences, The University of British Columbia, Vancouver, British Columbia, Canada (R.E.R.).

Purpose: Clinical studies with doxorubicin (DOX) or daunorubicin (DAUN) reveal variability in pharmacokinetic parameters and toxic effects. The cause of these variations is unknown; however, alterations in the activity of enzymes that metabolize these anthracyclines, aldo-keto reductases (AKRs) and carbonyl reductases (CBRs), may be a contributing factor. Currently, there are conflicting reports in the literature on the toxicity of the parent drugs and their major metabolites.

Methods: Therefore, we sought to find a correlation between metabolic activity and drug toxicity using 9 cell lines. Metabolic studies involved introducing 10 μM of DOX or DAUN to cell cytosols and measuring production of the major metabolites, daunorubicinol (DAUNol) and doxorubicinol (DOXol), *via* UPLC/MS/MS.

Results: Tukey-Kramer multiple comparison statistical tests revealed four cell lines [liver (HepG2), colon (Hct-15), lung (H-460), and kidney (A-498)] as high metabolizers of DOX (ranging from 9.0±1.9 to 10.0±1.5 pmol DOXol/min•mg cytosolic protein) and DAUN (38.0±4.2 to 98.7±14.7 pmol DAUNol/min•mg) and five cell lines [heart (H9c2), prostate (PC-3), ovary (OVCAR-4), pancreas (Panc-1), and breast (MCF-7)] were categorized as low metabolizers (DOX: 4.0±1.0 to 5.1±0.8 pmol/min•mg; DAUN: 13.6±2.0 to 18.4±1.1 pmol/min•mg). The following reductases were analyzed for expression in the cell lines based on our previous findings that they metabolize DOX and DAUN, *in vitro*: AKR1A1, 1B1, 1B10, 1C1, 1C2, 1C3, 1C4, 7A2, CBR1, and 3. Western blots demonstrated that enzymes were significantly expressed in the high metabolizing cell lines (HMCLs) compared to the low metabolizing cell lines (LMCLs). Toxicity studies were conducted by incubating cell lines with 12 different concentrations of DAUN or DOX (0 to 150 μM) for specified time periods (6, 24, and 48 hr) and determining IC_{50} values using MTT cell proliferation assays. IC_{50} values at each time period were significantly higher for the HMCLs than the LMCLs. At 6 hr, the IC_{50} values suggest no significant difference in toxicity between DAUN and DOX for the HMCLs (DAUN: ranging from 34±3 to 52±4 μM; DOX: 30±4 to 45±6 μM) and the LMCLs (DAUN: 10±2 to 20±4 μM; DOX: 12±3 to

17±2μM). However, at 48 hr, DOX was found to be significantly more toxic than DAUN in both the HMCLs (DAUN: 15±2 to 19±6 μM; DOX: 3.0±0.5 to 6.0±0.9 μM) and LMCLs (DAUN: 2.0±0.4 to 6.0±0.9 μM; DOX: 0.40±0.05 to 1.0±0.3 μM).
Conclusion: Therefore, our results indicate a correlation between toxicity following DOX or DAUN exposure and metabolism by AKRs and CBRs.

6. Epoxyeicosatrienoic Acids Delay Mitochondrial Failure and Maintain their Morphology During in vitro Cellular Stress

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Purpose: Cellular excitation-contraction and mitochondrial energetics are tightly regulated in cardiac cells to meet the high energetic flux during cardiac work. Cellular stress conditions can result in mitochondrial functional and morphological changes influencing the energetic state of the cell. Epoxyeicosatrienoic acid (EETs), cytochrome P450 derived metabolites of arachidonic acid (AA), are involved in maintaining cardiac homeostasis and protection against cell injury. We aimed to further investigate EET-mediated protective mechanisms and their role in regulating mitochondrial activities during cellular stress.
Methods: Human fibroblast WI-38 cells and rat myocardial H9c2 cells were treated with 11, 12-EET (0 or 1μM) and subjected to different types of cellular stressors including hypoxia-reoxygenation (HR), acute doxorubicin (DOX) treatment and photodynamic stress (PD). Alteration in mitochondrial function and dynamics were monitored with a Zeiss Axio Observer Z1 epifluorescence microscope using mitochondrial specific probes; TMRE for visualizing changes in mitochondrial membrane potential ($\Delta\Psi m$), and MitoTracker Green for evaluating modifications in mitochondrial morphology comparing to the elongated form in control cells. Caspase-3 activity was determined in cytosolic fractions by monitoring the release of 7-amino-4-methylcoumarin (AMC) by proteolytic cleavage of the peptide Ac-DEVD-AMC (20μM).
Results: Significant mitochondrial depolarization during reoxygenation observed in control cells was prevented by EETs. Interestingly, DOX treatment resulted in both increased mitochondrial fragmentation and membrane depolarization. These effects were significantly reduced by EETs. The putative pan-EET antagonist, 14,15-EEZE, abrogated the EET protective effect in DOX mediated injury. EETs attenuated the activation of caspase-3, downstream effects of mitochondrial dysfunction, following DOX treatment. Similarly, EETs enhanced mitochondrial resistance and maintained their membrane potential and elongated morphology during photo-activated cytotoxicity.
Conclusion: Importantly, we demonstrate that EETs slowed the collapse of mitochondrial membrane potential following HR injury, DOX treatment and PD stress. Moreover, EETs minimized mitochondrial fragmentation induced by DOX and PD treatments. Together these data suggest EETs can enhance mitochondrial function against cellular stress and improve their survival.

7. Synthesis and Characterization of Carboxylic Acid and Amine Surface-conjugated, Hydrophobically Derivatized Hyperbranced Polyglycerols for Use as Potential Nanoparticulate Drug Carriers

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Purpose: Current therapy of superficial bladder cancer involves the instillation of chemotherapy agents directly into the bladder after tumor resection. However, urine dilution of the drug and voiding after 2 hours results in poor drug uptake, reduced efficacy and high recurrence rates. It has been suggested that the use of mucoadhesive drug delivery systems may prolong the contact time of the drug with the bladder wall to increase drug uptake. Functional groups such as carboxylates, amines and thiols have been shown to possess mucoadhesive properties. The purpose of this study was to synthesize a series of hyperbranched polyglycerols (HPGs) with (C_8 – C_{10}) alkyl derivatized cores that bind anticancer taxane drugs. These HPG's were

then modified with MePEG and surface conjugated with mucoadhesive carboxyl or amine moieties. The physiochemical characteristics, cytotoxicity, and cell binding ability of these HPG's were then determined.

Methods: HPGs with surface MePEG chains (HPG-MePEG) were synthesized by addition of MePEG 350 to the reaction by ring-opening polymerization. These polymers were further functionalized with amine (HPG-MePEG-NH2) and carboxylic acid (HPG-MePEG-COOH) groups. All HPGs were characterized in terms of NMR, FT-IR, particle sizing, thermal properties, cytotoxicity to KU-7 bladder cancer cells and cell binding ability.

Results: All HPGs structures were confirmed by NMR and FT-IR spectra. All of these nanoparticulate polymers were unimolecules with a size between 5-10nm. Most of these polymers were water-soluble (greater than 100mg/mL). *In vitro* cytotoxicity showed that these polymers were not toxic to a KU-7 cell line. Cell binding and uptake studies demonstrated that HPG-MePEG-NH_2 showed a strong binding and rapid uptake to KU-7 cells.

Conclusions: HPG's may be successfully modified with MePEG and mucoadhesive moieties to give freely soluble nanoparticulate drug carriers. These polymers are non toxic, do not aggregate in solution and the amine-derivatized polymer, in particular, demonstrated great potential as a cell adhesive carrier of hydrophobic anticancer drugs.

8. Non-ulcerogenic Effective Non-steroidal Anti-inflammatory Prodrugs of Aspirin, Ibuprofen, and Indomethacin: Is Nitric Oxide-release Required?

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Purpose: As part of an on-going medicinal chemistry program aimed to develop new nitric oxide-releasing non-steroidal anti-inflammatory drugs (NO-NSAIDs) devoid of gastrointestinal and cardiovascular side-effects, our purpose was to evaluate the anti-inflammatory activity and ulcerogenicity of two groups of new hybrid NO-NSAIDs possessing tyrosol, 3-hydroxybenzyl alcohol (3-HBA), or 4-hydroxybenzyl alcohol (4-HBA) as linkers between the carboxylic acid group of an aspirin and the nitric oxide-releasing moiety (a *N*-diazeniumdiolate).

Methods: Ester prodrugs were formed by simple nucleophilic displacement reactions between tyrosol, 3-HBA, or 4-HBA with the corresponding NSAID (aspirin or ibuprofen) acid chloride dissolved in tetrahydrofuran (THF). All prodrugs were screened for anti-inflammatory activity *in vitro* (ovine COX-1 and human recombinant COX-2 immunoassay) and *in vivo* (carrageenan-induced rat paw edema assay). Additionally, aspirin and ibuprofen prodrugs were tested for ulcerogenicity (ulcer index assay).

Results: We could not find a direct correlation between COX enzyme activity and prodrug concentration (0.001-100 μM) in two different experiments, which is characteristic of inactive molecules; however, during the course of our investigation, when we administered the experimental ester prodrugs (714 μmoles/kg) orally to Sprague-Dowley rats, we were surprised to see an equivalent or even improved *in vivo* anti-inflammatory activity (41-68 % decrease in inflammatory response) compared to the parent drugs (50% decrease) and a significant reduction in ulcerogenicity by NSAID prodrugs without the nitric oxide-releasing moiety. This result is in disagreement with recent reports described in the literature, describing the essential role of NO-releasing groups to avoid the formation of gastric ulcers.

Conclusion: Originally, the purpose of forming hybrid ester prodrugs possessing a NO-releasing group was to release the active components (namely the NSAID and NO) after metabolic activation, and NO was supposed to protect the gastric epithelial layer by counteracting the mechanism-based toxicity of the corresponding NSAID. When we observed that simple esters of aspirin and ibuprofen maintained the desired anti-inflammatory effect, but were devoid of gastric toxicity, we decided to change our approach and cancel the attachment of NO-releasing groups to study the role of simple phenol moieties to circumvent the unwanted gastrointestinal side-effects observed in the long-term administration of NSAIDs. These results may provide preliminary evidence to support the use of *simple* aspirin and ibuprofen ester prodrugs as effective anti-inflammatory agents without gastric ulcerogenic potential, without the need for additional NO-releasing moieties. To validate these results, we are evaluating the biological properties of similar indomethacin prodrugs. Indomethacin (a selective COX-1 inhibitor) is a much more potent anti-inflammatory agent compared to aspirin and ibuprofen, but it is also more ulcerogenic. If we

confirm that in fact, simple ester prodrugs of indomethacin possessing tyrosol, 3-HBA, or 4-HBA are as potent as indomethacin, but are devoid of gastric side-effects, this would constitute a major breakthrough in the development of safe anti-inflammatory agents.

9. Mercury Modulates the CYP1A1 at Transcriptional and Posttranslational Levels in Human Hepatoma HepG2 Cells

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Purpose: We have previously demonstrated that mercury (Hg^{2+}) potentiates the 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD)-mediated induction of Cyp1a1 at transcriptional and posttranslational levels in murine hepatoma Hepa 1c1c7 cells. Therefore, it is crucial to investigate whether similar effects will occur in the human hepatoma HepG2 cells.
Methods: We examined the effect of Hg^{2+} on the expression of aryl hydrocarbon receptor (AhR)-regulated gene, cytochrome P450 1A1 (CYP1A1) at all steps of the AhR signaling pathway. For this purpose HepG2 cells were incubated with TCDD (1 nM) in the presence and absence of various concentrations of Hg^{2+} (2.5, 5 and 10 μM). CYP1A1 mRNA, protein, and activity levels were measured using real-time PCR, Western blot, and 7-ethoxyresorufin *O*-deethylase analyses, respectively.
Results: Our results showed Hg^{2+} significantly inhibited the TCDD-mediated induction of CYP1A1 at the mRNA, and protein levels at the highest concentration tested (10 μM). Of interest, Hg^{2+} caused a concentration-dependent inhibition of CYP1A1 at the catalytic activity level. At the transcriptional level, co-exposure to Hg^{2+} and TCDD significantly decreased the TCDD-mediated induction of AhR-dependent luciferase reporter gene expression. Moreover, Hg^{2+} did not affect CYP1A1 mRNA stability while decreasing its protein half-life contributing to the inconsistency between catalytic activity and transcriptional level and suggesting the involvement of a posttranslational mechanism. Importantly, Hg^{2+} increased the expression of heme oxygenase-1 (HO-1), a rate limiting enzyme in heme degradation. Interestingly, the HO-1 inhibitor, tin mesoporphyrin prevented the decrease in TCDD-mediated induction of CYP1A1 activity by Hg^{2+}, suggesting a direct role of HO-1 in the modulation of CYP1A1 at catalytic activity level.
Conclusion: We demonstrated that Hg^{2+} down-regulates the expression of CYP1A1 at transcriptional, and posttranslational levels in HepG2 cells. In addition, HO-1 and protein degradation by Hg^{2+} are partially involved in the modulation of CYP1A1 at posttranslational level.
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10. Modulation of NAD(P)H:Quinone Oxidoreductase by Vanadium in Human Hepatoma HepG2 Cells

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Purpose: We have previously shown that vanadium (V^{5+}), significantly modulate the expression of NAD(P):quinone oxidoreductase 1 (Nqo1) in the murine hepatoma Hepa 1c1c7 cells. Therefore, it is important to investigate whether similar changes occur in humans.
Methods: In the current study we examined the effect of V^{5+} (as ammonium metavanadate, NH_4VO_3) on the expression of NQO1 at each step of signal transduction pathway in human hepatoma HepG2 cells. In an attempt to examine these effects, HepG2 cells were treated with increasing concentrations of V^{5+} in the presence of two NQO1 inducers, the 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) and isothiocyanate sulforaphane (SUL).
Results: Our results showed that V^{5+} induced the production of reactive oxygen species (ROS) in a dose-dependant manner, and thus it is expected that this oxidative stress will have effect on the ability of V^{5+}, to induce NQO1. Surprisingly, we observed that V^{5+} inhibits the TCDD- and SUL-mediated induction of NQO1 at mRNA. Therefore, the observed inhibition was reflected at protein, and catalytic activity levels. Investigating the effect of V^{5+} alone or in the presence of TCDD or SUL at transcriptional levels revealed that V^{5+} significantly inhibited TCDD- and SUL -mediated induction of ARE-dependent luciferase reporter gene expression. At transcriptional level, we showed that V^{5+} was able to decrease the TCDD- and SUL-induced nuclear accumulation of nuclear factor erythroid 2-related factor-2 (Nrf2) without affecting Nrf2

mRNA level or protein levels. Looking at the post-transcriptional level, V^{5+} did not affect NQO1 mRNA stability, thus eliminating the possible role of V^{5+} in modifying NQO1 gene expression through this mechanism. On the other hand, at post-translational level, V^{5+} was able to significantly decrease NQO1 protein half-life.

Conclusion: The present study demonstrates that V^{5+} down-regulates NQO1 at the transcriptional level in the human hepatoma HepG2 cells by AhR- and Nrf2-dependent mechanisms.

Acknowledgements: This work was supported by NSERC Discovery Grant RGPIN 250139-07 to A.O.S. G.A. is the recipient of Egyptian government Scholarship award.

11. Effects of Growth Hormone and Therapeutic Ultrasound on Male Sprague Dawley Rats' Mandible

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Purpose: Previous studies have shown that both growth hormone (GH) and low intensity pulsed ultrasound (LIPUS) can enhance condylar cartilage growth and bone formation. The aim of this study is to evaluate the synergistic effect of both local injections of GH and LIPUS application on mandibular growth in rats.

Methods: Twenty four male Sprague Dawley rats (200g body weight) were divided into four groups, 6 animals each. Group 1 was treated with recombinant rat GH (rGH=5µg daily), group 2 was treated with LIPUS (20 minutes daily), group 3 was treated with both rGH (5µg daily) and LIPUS (20 minutes daily), and control group did not receive any treatment. Local administration of rGH and LIPUS were performed to the posterior attatchment of the mandibular condyle. After 21 days of daily treatment, all the groups were euthanized; the mandibles were dissected, and scanned by Micro-Computed Tomography (MicroCT) to measure the mandibular bone volume and mandibular bone surface area. Also real-time polymerase chain reaction (RT-PCR) was performed to assess the already reported GH markers' (c-fos, c-jun, and IGF-1) expression.

Results: Groups 1 and 2 showed similar growth stimulation when compared to the control group. Also, group 3 showed that GH and LIPUS have complementary effect on mandibular growth when compared to the control group. However, there was no statistical significant difference between groups 1, 2 and 3 with regard to bone volume or surface area. Moreover, the RT-PCR showed that the expression of c-jun in harvested livers for Group 3 was less than that of Group 1, confirming that the action of LIPUS has minimized the effect of GH. The other two markers did not show any change in gene expression compared to control.

Conclusion: When rGH was locally injected into the posterior attachment of the mandibular condyle in rats together with LIPUS application, complimentary mandibular condylar growth changes occurred along with less potential side effects.

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12. Inflammation Downregulates Angiotensin Converting Enzyme 2 in Rat Heart

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Purpose: Angiotensin Converting Enzymes, ACE and the newly discovered ACE-2, are important enzymes involved in the renin angiotensin system (RAS). ACE and ACE-2 catalyze different biological reactions and the balance between their activities is important for regulation of blood pressure as well as the fluid and electrolyte homeostasis. ACE-2 knockout mice did have severe cardiac impairment suggesting the cardioprotective function of ACE2 and its role in cardiovascular diseases. Inflammatory diseases like rheumatoid arthritis are associated with increased risk for cardiovascular complications. The role of ACE and ACE-2 in inflammatory disease has not been studied before. We studied the effect of inflammation on the expression levels of ACE and ACE-2 in 2 groups (n=4/group) of Inflamed pre-adjuvant arthritis (AA) and Control (healthy) male Sprague-Dawley rats.

Methods: The inflamed group received 0.2 ml of 50 mg ml^{-1} *Mycobacterium butyricum* suspended in squalene into the tail base. On day 12, rats were euthanized and their organs (hearts, liver, kidney and intestine) were excised. mRNA of ACE and ACE-2 were determined by real time polymerase chain reaction RT-PCR. ACE and ACE-2 protein expression in rat heart was determined by western blot.

Results: ACE and ACE2 mRNA were more pronounced in the intestinal tissue and heart than in the kidney. Inflammation resulted in more than 80% reduction of ACE-2 mRNA and protein in rat heart. On the other hand, ACE did not significantly change.
Conclusion: ACE2 has been found to provide negative feedback of RAS and protection of the heart and kidneys. Disruption of the balance between ACE and ACE2 observed in inflammation may be, at least in part, involved in the cardiovascular complications seen in patients with inflammatory diseases.

Drug Delivery and Pharmaceutical Technology

13. Contramid® Microcapsules: A Versatile Platform for Drug Delivery

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Purpose: Contramid® is a versatile cross-linked high amylose starch that may be converted to a variety of pharmaceutical presentations to enable oral delivery. The objective of this work was to demonstrate the ability to spray dry Contramid® to form hollow microcapsules that can entrap drugs, flavours, vitamins, and probiotics yielding sustained-release, taste masked, simple powders suitable for capsule filling or tableting.
Methods: Contramid® suspensions containing tramadol hydrochloride, caffeine, menthol or *Lactobacillus Rhamnosus* as model agents were spray dried using a Niro P6.3 spray dryer at various inlet and outlet temperature combinations.
Results: The resulting dry powders comprising 10-50 micron Contramid® particles were shown by scanning electron microscopy to be hollow porous granules containing up to 30% wt/wt of the drug, flavour or vitamin within their lumen. In vitro dissolution tests with drug or flavour loaded Contramid® microcapsules demonstrated sustained release of these agents for up to 4 h; encapsulation in Contramid® microcapsules also enabled significant taste masking. Studies using *Lactobacillus Rhamnosus* demonstrated the bacteria could be successfully encapsulated by spray-drying resulting in a 100% recovery of viable counts post re-suspension.
Conclusion: Contramid® microcapsules offer a simple, cost-effective and versatile platform for encapsulation sustained release and taste masking, of sensitive agents such as drugs, probiotics and flavours.

14. Preparation and Optimization of Estradiol Loaded PEGylated Nanoliposome as a Potential Vascular Delivery System for the Treatment of Restenosis

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Purpose: Local delivery of anti-restenosis drugs encapsulated in biodegradable nanoparticulate systems with sustained release characteristics offers a potential therapeutic approach to reduce restenosis following coronary angioplasty. Nanoliposome would be a promising drug delivery system at the site of injury, while the biocompatible nature of liposome membranes may reduce the inflammation and proliferation observed after stent application due to the interaction of the endothelium with the polymeric stent coat and /or polymeric nanoparticles. Estrogen has shown promising effects in inhibition smooth muscle cell proliferation and migration and accelerating reendothelialization. As macrophage content is significantly larger in lesions at the time of coronary angioplasty and conventional liposomes are readily taken up by cells of the reticuloendothelial system, therefore PEGylated nanoliposome encapsulating estradiol was prepared and optimized by means of an experimental design in the present study.
Methods: Response surface methodology (RSM) based on D-optimal design was applied for formulation optimization. Type of main lipid, lipid to drug molar ratio and cholesterol proportion were selected as the independent variables while the incorporation efficiency of the liposomes as the dependent variable. Different formulations were prepared by hydration method followed by sonication. The size and zeta-potential were measured by particle size analyzer and zeta-potentiometer, respectively. The stability and two-week release profile of optimum formulation were also studied.

Results: Incorporation of estradiol was higher in egg phosphatidylcholine liposomes, whereas the drug was displaced from liposomes, as the cholesterol content of liposome membranes increased. The optimum formulation of estradiol nanoliposomes composed of egg phosphatidyl-choline (PC)/distearoyl phosphatidylglycerol (DSPG)/distearoyl phosphatidylethanolamine-PEG2000 (DSPE-PEG) with a molar proportion of 8.5:1:0.5 and lipids/drug molar ratio of 30, without cholesterol, had higher incorporation efficiency (91 ± 2%). The prepared optimum vesicles had sustained in vitro release profile showing about 15% drug release after two weeks. The size of liposomes was uniform with an average diameter around 121.5 ± 11.3 nm.

Conclusion: In order to local therapy of restenosis, estradiol loaded PEGylated nanoliposomes with appropriate in vitro characteristics was prepared in this study. The proposed nanoliposome system has dual action: as a drug releasing depot and biocompatible nanoparticulates which may reduce the problems caused by non-degradable as well as biodegradable polymers.

15. Magnetic Drug Targeting to the Eye

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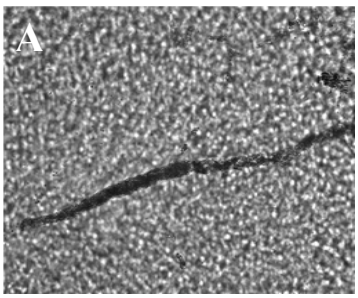
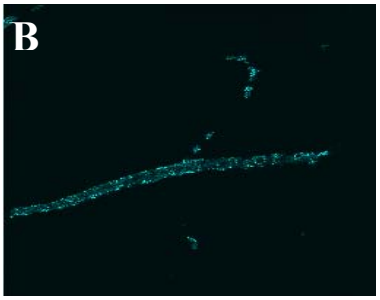
Purpose: Drug delivery to the eye is currently limited to either topical application on the cornea or by injection into the vitreous. These routes of delivery have shortcomings; topical applied drugs can only reach the anterior section of the eye, while injection of the drug can cause trauma of the eye, which induces more complications. Magnetic drug delivery could be a viable alternative for ocular drug delivery. Drugs bound to magnetic particles can be injected directly into the bloodstream, and concentrated in the eye with the use of a magnetic field. This enables us to direct drugs to tissues in the posterior section of the eye, which cannot be safely reached by other delivery strategies. In this study, it was attempted to direct magnetic particles in the bloodstream to the eye.

Methods: Cobalt (size 50 nm) and magnetite (size 1 μm) particles were radiolabeled with ^{99m}Tc for biodistribution study purposes. The magnetic particles were injected into the tail vein of C57BL/6 mice. Simultaneously, a magnetic field was created near the eyes by placing a magnet directly above the eyes of the mice to attract the administered particles. After 30 min of treatment, the mice were sacrificed and organs were removed for radioactive biodistribution and histological studies. Confocal microscopy was used to visualize particles in cross-sections of the eye, retinal whole mounts and the liver.

Results: Radioactive biodistribution studies indicated slightly increased particle activity in the eyes of mice treated with a magnetic field compared to non-magnet treated mice. Confocal imaging showed some particle deposits in retinal blood vessels (Figure 1A, B). Particles were mainly present in the liver (~30% of total amount), which was reflected by confocal microscopy (Figure 1C).

Conclusion: Magnetic particles were encountered in the retinal blood vessels. The particles most likely cannot cross the blood retinal barrier (BRB), which has similar characteristics as the blood brain barrier. Uptake through to BRB can be facilitated by binding membrane permeant peptides (such as TAT) to the particles. Low particle presence in the eye can also be attributed to the minimal amount of blood flow through the eyes; administration via the carotid artery can increase particle concentrations in the blood passing through the eyes. These preliminary results show the potential of magnetic particles for ocular drug delivery.





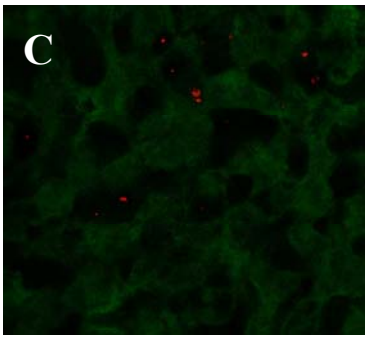


Figure 1. A) Blood vessel situated in the retinal layer. B) Confocal microscopy reveals magnetic particles present in the blood vessel. C) Particles (red) present in liver tissue.

16. Synthesis and *in vitro* Evaluation of Peptide Decorated Polymeric Micelles for Paclitaxel Delivery to Human Cancer Cells

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Purpose: The aim of this study is to develop polymeric micellar delivery systems decorated with either p160, c(RGDfK) on their surface and compare the efficacy of these functionalized polymeric carriers in paclitaxel (PTX) delivery to human cancer cells MDA-MB-435.
Methods: Acetal-poly(ethylene oxide)-*b*-poly(ε-caprolactone) (Acetal-PEO-*b*-PCL) was synthesized by ring opening polymerization of ε-caprolactone using Acetal-PEO as initiator and stannous octoate as catalyst. After micellization, the acetal groups on the surface of polymeric micelles were converted into aldehyde by acidification. Through Schiff base formation, the peptides p160 or c(RGDfK) were conjugated to the aldehyde bearing micelle. The conjugation efficiency of the peptide was determined using gradient reversed phase HPLC. PTX was physically encapsulated into the prepared micelles using dialysis technique. The hydrodynamic diameters as well as the polydispersity index of paclitaxel loaded micelles were estimated using Dynamic light scattering (DLS). The *in vitro* cytotoxicity of PTX loaded formulations as well as free PTX against MDA-MB-435 cells was assessed using MTT assay.
Results: Functionalized micelles decorated with either p160 or c(RGDfK) peptides were successfully prepared. Reversed phase HPLC showed complete conjugation of the added peptides to the micellar surface, and revealed 20% and 17% peptide molar conjugation level for p160 and c(RGDfK), respectively. DLS showed an average hydrodynamic diameter of 76.2 and 92.9 nm for paclitaxel loaded p160-PEO-*b*-PCL and c(RGDfK)-PEO-*b*-PCL, respectively. At concentrations below the cmc value of the polymer, the PTX loaded formulations did not show any significant difference in cytotoxicity compared to the free PTX against MDA-MB-435 human cancer cells. However, above the cmc value, an increased cytotoxicity for the encapsulated PTX in p160 and c(RGDfK) decorated micelles in comparison to free PTX was revealed. Compared to free PTX, conjugation of p160 and c(RGDfK) to micellar shell significantly increased the cytotoxicity of encapsulated hydrophobic PTX by 6.8% and 9.9 %, respectively. The enhanced cytotoxicity of these functionalized micelles compared to free PTX could be explained by the enhanced solubility of the poorly soluble PTX in the micelle solution, increased stability of the cytotoxic PTX inside the micelle core, and/or better uptake of PTX micelles by the cells.
Conclusions: The results points to a potential of p160, c(RGDfK) modified polymeric micelles for active drug targeting to human cancer cells.
Acknowledgments: Mostafa Shahin acknowledges funding by Frederick Banting and Charles Best CGS Doctoral Award/CIHR and Egyptian Government Scholarship.

17. Developing a Microemulsion with Potential for Pharmaceutical Applications: Formulation, Characterization, Sterilization, and *In Vitro* Cell Culture Studies

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Purpose: The purpose of this research project was to develop sterile water-in-oil (w/o) microemulsions

using dioctyl sodium sulfosuccinate (DOSS), ethyl oleate (EO), and water.

Methods: Compositions of surfactant, oil, and water that formed visually clear microemulsions were identified by titrating DOSS-EO mixtures with water and plotting the observed phase behavior on a ternary phase diagram. The formation of w/o microemulsions was further verified via polarized light microscopy and electrical conductivity measurements. Stable microemulsions were evaluated using dynamic light scattering (DLS) and rheological experiments. Formulations that demonstrated desirable physico-chemical properties were prepared using aseptic technique and sterilized by membrane filtration. The sterilization method was validated via two methods (filtration and direct inoculation), plating on blood agar, and using *E. Coli* as the positive control. The safety of these formulations was studied in NIH 3T3 mouse fibroblast cell lines using a neutral red cell viability assay.

Results: DOSS-EO mixtures were able to incorporate up to 14 % w/w water in a transparent and stable microemulsion. Polarized light microscopy of microemulsions did not exhibit optical birefringence. Microemulsions demonstrated a composition dependent change in electrical conductivity. All microemulsions possessed conductivity values approximately equal to 0.05 μSiemens/cm indicating formation of w/o systems. DLS measurements of microemulsions demonstrated the presence of nanometer sized droplets in the range of 4 nm to 18 nm in diameter. As is expected of true microemulsions, all tested formulations demonstrated Newtonian flow properties. Microemulsions prepared aseptically and filtered using membrane filters showed no bacteria on gram-stained slides. The membrane filtration method for sterilizing the microemulsion was validated when no microbial growth was seen up to 14 weeks after preparation of the formulations. The viability of mouse fibroblasts was influenced significantly by the amount of surfactant present in the formulations.

Conclusions: Stable w/o microemulsions were prepared using pharmaceutically relevant components. Development and validation of an aseptic method for preparation and sterilization of the formulations extends its potential utility to ophthalmic and parenteral routes of drug delivery. *In vitro* toxicity testing in mouse fibroblast cell lines demonstrate that these formulations are well tolerated in biological systems.

18. Development and Evaluation of Dual Loaded Nanoparticles for Periodontal Infections

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Purpose: The periodontal diseases are highly prevalent and can affect up to 90% of the worldwide population. The present study was aimed at the formulation and evaluation of dual loaded biodegradable nanoparticles of sparfloxacin and flurbiprofen for the treatment of periodontal diseases. The dual loaded nanoparticles would serve dual function of reduction of micro-organism in periodontal pocket as well as modulation of host inflammatory response which would be a milestone for dental therapeutics.

Methods: 1. Formulation of Dual loaded Nanoaparticles: The nanoparticles were prepared by single emulsification-solvent evaporation method using PLGA as the polymer. In order to optimize the formulation various parameters like polymer: drug ratio, polymer concentration, stirring speed and aqueous/ organic phase ratio were altered and their effect on the drug entrapment, drug loading and particle size was evaluated.

2. Evaluation of Dual loaded Nanoaprticles: a) Drug loading and entrapment efficiency: Drug loading was calculated by dividing the amount of drug in nanoparticles by the amount of nanoparticles recovered. The entrapment efficiencies (EE) can be calculated with the percent ratio of the actual amount of drug incorporated into nanoparticles to the total amounts of drug used. b) Surface morphology, Particle size, size distribution and Zeta potential: Transmission electron microscope (TEM) was used for morphology studies. Diffraction light scattering was used for particle size and polydispersity index measurements. d) *In vitro* drug release studies of Dual loaded Nanoparticles: 20 mg of nanoparticles in 5 ml of phosphate buffer pH 7.4, were introduced into dialysis bag and put into 100 ml glass beaker containing 25 ml of dissolution medium maintained at 37 ± 2.0˚C in a water bath shaker. At predetermined time interval, release medium was withdrawn and concentrations of released sparfloxacin and flurbiprofen were measured with UV spectrophotometer at 247.5 nm and 290 nm.

Results: Formulation NPED1 containing 10:1 polymer: drugs ratio, 4:1 aqueous/organic phase ratio and 1% PVA exhibited acceptable particle size,

entrapment efficiency and high theoretical drugs loading and was chosen as the optimized formulation. Drug loading of the optimized formulation NPED1 was found to 4.45% and 4.98% for flurbiprofen and sparfloxacin, respectively. Entrapment efficiency of the optimized formulation was found to 75.0 % and 85.3 % for flurbiprofen and sparfloxacin, respectively. The mean particle size, polydispersity index and zeta potential values were found to be 324 nm. 0.184 and -15mV respectively. After higher initial burst release for flurbiprofen and sparfloxacin (37.9 % & 42.43 %) a sustained release of the drugs from the prepared formulation was observed. A cumulative % drug release of 75.81 % and 79.6 % was observed after 6 days for flurbiprofen and sparfloxacin respectively. After fitting the *in vitro* data into release models a diffusion controlled release of drugs from the nanoparticles was observed.

Conclusion: The dual loaded nanoparticles containing sparfloxacin and flurbiprofen for the treatment of periodontal diseases were successfully prepared and evaluated. The optimized formulation was satisfactory in terms of drug loading, entrapment efficiency, particle size, particle size distribution, polydispersity index, surface morphology and *in vitro* release.

19. Effect of Polymer Blend on Diltiazem HCl Matrix Tablets Prepared by Direct Compression

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Purpose: The deformation mechanism of pharmaceutical powders, used in formulating directly compressed matrix tablets, affects the characteristics of the formed tablets.

Methods: Three polymers of different deformation mechanisms were tested for their impact on Deltiazem (DZ) directly compressed tablets namely Kollidon ® SR (KL SR, plastic deformation), Ethylcellulose (EC, elastic deformation) and Carnauba wax (CW, brittle deformation) at different compression forces.

Results: Tablets based mainly on KL SR, the plastically deformed polymer (DZ1) exhibited the highest hardness values compared to the other formulae which based on either blends of KL SR with CW, the very brittle deformed polymer. The upper detected force for DZ formulae and the lower punch force were found to dependent mainly on the powder deformation. This difference is attributed to the work done during the compression phase as well as the work lost during the decompression phase. Furthermore, the release profiles of DZ from formulae DZ 2 and DZ 4 that based on the composition (2KL SR: 1EC) and (1KL SR: 2EC), respectively, were consistent with different deformation mechanisms of KL SR and EC and on the physicochemical properties like the water absorptive capacity of EC. Upon increasing the weight ratio of KL SR (DZ), the release rate was greatly retarded.

Conclusion: The design of directly compressed matrix tablets for sustained release properties should take into consideration the deformation mechanism of used polymers. In addition, the critical parameters such as tabletting conditions, compression forces, upper and lower punch compression forces, hardness, tensile strength and friability will be affected according to the deformation mechanism such polymers.

20. Preparation and Quality Evaluation of an Extemporaneous Enteric-release Liquid Formulation of Lansoprazole for Oral Administration

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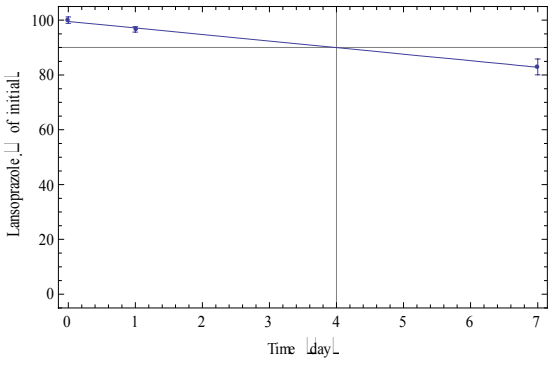
Purpose: Lansoprazole is used for the treatment of hyperacidity-related conditions. It is commercialized as an enteric-release tablet. For pediatric administration, current practice is to dissolve the formulation in a bicarbonate solution, resulting in an immediate-release preparation. We propose a novel extemporaneous enteric-release liquid formulation of lansoprazole for oral administration.

Methods: The formulation was prepared from 30 mg lansoprazole tablets (Prevacid Fastab, Abbott Canada) at a concentration of 3 mg/mL. A stability-

indicating HPLC method was developed to quantify the lansoprazole. Content uniformity of 10 mL samples of a 100 mL batch (n=10) was evaluated. Dissolution was evaluated based on the USP method for enteric formulations. Assay of lansoprazole was evaluated after 0, 1 and 7 days at 25°C. Suitability for nasograstric administration was also evaluated using different tubes.

Results: HPLC method had a LOQ of 6.5 ng/injection (n=6, RSD 2.7%). Precision was 0.35% RSD for 100% label claim samples (0.65 µg/injection, n=6). Stability of the HPLC samples in the auto-sampler was confirmed by reinjection after 24h at 5°C. No peak interference was observed between lasoprazole and the forced degradation products (HCl 0.1N). No interference was observed between lansoprazole and the inactive ingredients. Calibration curve was performed to cover a range of 1% to 150% of label claim (n=15, r^2 = 0.99998). Formulation did not block 6 FR or larger nasogastric tubes. Enteric-release profile was confirmed by the dissolution method. Assay results from 0, 1 and 7 day stability samples were interpolated by linear regression (r^2 = 0.997). Based on the interpolation results, 10% degradation (relative to time zero assay) is predicted after 4 days at 25°C (see Figure).

Conclusion: An extemporaneous enteric-release liquid formulation of lansoprazole for oral administration was successfully developed. This formulation maintains the enteric dissolution profile observed with the commercial formulation. The formulation is easy to prepare and maintains its critical quality attributes including assay, dissolution, content uniformity and suitability for nasogastric administration. Further testing will be performed to confirm the interpolated results.



21. Nanoformulation Development and Pharmacometrics of the Histone Deactylase Inhibitor, Vorinostat

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Purpose: To develop and validate an isocratic LC/MS method for detect of Vorinostat (SAHA), devise a micellar formulation for intravenous (IV) administration to rats; delineate the pharmacokinetics of this formulation; and examine the pharmacologic activity of vorinostat.

Methods: A LC/MS method using a Phenomenex® Luna® $C_{18}(2)$ column was utilized to detect vorinostat. The mobile phase consisted acetonitrile, water, and formic acid (30:70:0.1, v/v/v) at a flow rate of 0.60 mL/min with daidzein utilized as the internal standard. Detection was achieved with positive selected ion monitoring (m/z 265 for vorinostat; 255 for daidzein). A polymer (polyethylene glycol (PEG)-b-poly(D,L-lactide (PDLLA) 5000/3000) or PEG 400 was utilized to solubilize vorinostat. The micellar formulation produced average 144 nm in diameter micelles. Vorinostat was administered intravenously to cannulated male Sprague-Dawley rats at 10 mg/kg in either PEG-b-PDLLA micelles or in PEG 400. Serum and urine samples were collected from 0-120 h post-dose. Pharmacological activities of vorinstat were studied *in vitro* over the concentration range of 0-100 µg/mL: cytotoxicity in A375, HCT-116, HepG2, MDA-MB-231, and PC3 cancer cell lines; anti-adipogenic activity in 3T3-L1 cells; inhibition of cyclooxygenase-1; and antioxidant capacity.

Results: A novel LC/MS method for the detection of vorinostat was developed with linearity over 0.05-50 µg/mL being observed. The PEG-b-PDLLA nanoformulation increased water solubility of vorinostat by 15 times to 1.5 mg/mL. Alterations in pharmacokinetic parameters were seen between vorinistat in PEG-b-PDLLA micelles and vorinostat in PEG 400. These included a 3.1 fold increase in serum $t_{1/2}$, a 1.4 fold increase in AUC, a 1.5 fold decrease in V_d, and 3.7 fold decrease in CL_t. From positive SIM monitoring, a hydrolysis metabolite was detected in serum and urine with decreased levels seen in PEG-b-PDLLA samples. Vorinostat

was shown to possess other pharmacological activities including antioxidant, cytotoxic, and COX-1 inhibitory activities but had limited anti-adipogenic activity.
Conclusions: A sensitive, reproducible, and accurate method was developed for the detection of Vorinostat using LC/MS. A micellar formulation was developed with prolonged circulation in plasma and reduced metabolite formation. Vorinostat possesses additional pharmacological activity in addition to its HDAC inhibition.

22. Mechanistic Action and Disposition and Crystalline Polymorphisms of Oxyresveratrol

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Purpose: Develop a HPLC method to quantify oxyresveratrol in biological fluids; evaluate the oral and IV pharmacokinetics of oxyresveratrol in a rat model; examine the pharmacological activity of oxyresveratrol; delineate a newly discovered crystalline polymorph of oxyresveratrol anhydrous and dihydrate.
Methods: The conditions of the assay are as follows: a C_{18}(2) column, mobile phase composed of water, acetonitrile, and formic acid (70:30:0.04 v/v/v) at a flow rate of 0.6 mL/min, with ultraviolet detection at 320nm. Oxyresveratrol was administered either intravenously or orally to male Sprague-Dawley rats, and serum and urine collected over 120h post-dose. The pharmacological activity of oxyresveratrol was investigated over the concentration range of 0-250 µg/mL. The anti-proliferative activity of oxyresveratrol was examined using Alamar Blue in a variety of cancer cell lines (MDA-MB-231, HCT 116, and PC-3 cells). Ability of oxyresveratrol to inhibit oxidation of ABTS to $ABTS^{-+}$ by metmyoglobin was measured to investigate antioxidant acivity. Modulation of a deaceylated product due to histone deacetylase (HDAC) class 1 and 2 activity was monitored using a fluorescent based assay. The cyclooxygenase (COX) 1 and 2 inhibitory activity was examined using an ELISA to measure the reduction of COX-derived PGH_2 by SnCl2 $PGF_{2\alpha}$. A differential scanning calorimetry (DSC) was used to monitor the thermal events as a function of temperature increase.
Results: A novel and specific HPLC method was developed for oxyresveratrol. Oxyresveratrol was detected in plasma and urine primarily as glucuroconjugates. Oxyresveratrol demonstrates anti-proliferative activity, antioxidant capacity, inhibits HDAC activation, and has COX-1 and COX-2 inhibitory activity. The oxyresveratrol dihydrate showed a broad melting endotherm starting followed by another endotherm and an exotherm. The thermogram of oxyresveratrol anhydrous revealed its amorphous state showing an onset of glass transition temperature (T_{gi}) at 64°C and an end of glass transition temperature (T_{ge}) 67°C.
Conclusions: The method is sensitive, reproducible, accurate, and selective. The two forms of oxyresveratrol are physicochemically distinct as seen in differences in thermal events. Pharmacokinetic data indicates that oxyresveratrol is orally bioavailable, rapidly glucuronidated, and excreted renally and non-renally. Oxyresveratrol has a variety of pharmacological effects.

23. In vitro Diffusion of Epinephrine Nanoparticles Using a Flow-Through Diffusion System

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Purpose: To assess the in vitro diffusion of epinephrine nanoparticles. The use of epinephrine nanoparticles instead of epinephrine salt was hypothesized to enhance the sublingual bioavailability of epinephrine from a novel fast-disintegrating sublingual tablet formulation for the emergency treatment of anaphylaxis.
Methods: The diffusion of 80 µg epinephrine from four formulations, epinephrine base nanoparticles suspension (size 200 nm), epinephrine base suspension (33 µm), epinephrine base solution, and epinephrine bitartrate solution was studied over 8.5 hours using automated flow-through Franz cell system (n=6) with regenerated cellulose membranes (1000 MWt cutoff). Cumulative epinephrine

concentrations in the donor cell were measured using HPLC-UV. The cumulative epinephrine concentration versus time (AUC), maximum epinephrine flux (J_{max}) , time to reach *J*max (t_{Jmax}), and epinephrine permeation coefficient (Kp) for each formulation were calculated and statistically analysed using one-way ANOV and Tukey-Kramer tests, NCSS program, at a level of significance $p< 0.05$.

Results: The AUC and *J*max obtained from epinephrine nanoparticles, 10.4±1.7 µg/ml/hr and 15.1±1.9 µg/cm^2/hr respectively, were significantly higher than epinephrine suspension, 5.1±1.1 µg/ml/hr and 10.4±1.6 µg/cm^2/hr, epinephrine solution, 5.5±0.5 µg/ml/hr and 8.6±0.3 µg/cm^2/hr, and epinephrine bitartrate, 4.6±0.9 µg/ml/hr and 7.9±1.0 µg/cm^2/hr. t_{Jmax} was not significantly different between the four formulations. Kp of epinephrine nanoparticles, 0.19±0.07 cm/hr was significantly higher than epinephrine suspension, 0.13±0.002 cm/hr, epinephrine solution, 0.11±0.04 cm/hr, and epinephrine bitartrate, 0.10±0.04 cm/hr.

Conclusions: In this study, the permeation of epinephrine nanoparticles was almost 2 fold higher than the epinephrine bitartrate and epinephrine solution. Epinephrine nanoparticles may have the potential to enhance the sublingual bioavailability of epinephrine compared to epinephrine salt in the novel sublingual tablet formulation. The enhanced permeation effects of epinephrine nanoparticles on the sublingual absorption of epinephrine from rapidly disintegrating tablets will be confirmed using ex vivo and in vivo studies.

24. Antibody-mediated Osteoclast Targeting System using Calcitonin as a Model Drug

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Purpose: Degenerative bone disease is often the result of rapid adaptive remodeling, due to the activation of bone resorbing osteoclasts (OC). However, current antiresorptive therapies do not directly target OCs, and rely on systemic administration in quantities sufficient to elicit a therapeutic response upon bone cells. As antibodies have exquisite target recognition specificity, we hypothesized that monoclonal antibody (mAb) generated against Receptor Activator of Nuclear factor Kappa B receptors (RANK) found on OC would selectively target and/or deliver conjugated antiresorptive drug cargo to OC. Hence, we developed an anti-RANK mAb-mediated delivery system as a "universal OC targeting platform", initially using Salmon Calcitonin (sCT) as the model drug.

Methods: mAb was generated by immunizing mice with RANK. Serum antibody titer was measured by ELISA; splenocytes were collected and fused with SP2/0 myeloma cells. Hybridomas were screened by ELISA and mAbs were purified by affinity chromatography and dialysis, quantified by UV Spectroscopy and Bicinchoninic protein assay (BCA), and characterized by SDS-PAGE. Their receptor binding affinity was determined by ELISA and antigenic specificity by Western Blot. To synthesize sCT-mAb bio-conjugates, thiol groups were generated in mAb using 2-Iminothiolane and reacted with sCT-PEG-MAL synthesised from sCT and NHS-PEG-MAL. Conjugates were purified by dialysis, assayed by BCA, characterised by SDS-PAGE and ELISA for sCT on RANK coated plates using anti-Calcitonin antibodies. To test their OC targeting potential, OCs were generated from RAW 264.7 cells and their functionality was confirmed by tartarate resistant acid phosphatase (TRAP) activity, TRAP staining and Resorption Pit assay.

Results: With SDS-PAGE, mAb appeared at 150 kD, with monoclonality and specificity for RANK in ELISA and subsequent Western Blot against immobilized RANK protein. sCT-mAb conjugates were evidenced as a band above 150 kD in SDS-PAGE. Receptor binding affinities and specifities of both mAb and sCT were maintained after conjugation. Similarly, generated OCs appeared as multinucleated cells, with seven fold higher TRAP activity compared to RAW cells. Intervention of OCs with sCT clearly reduced TRAP and calcium phosphate resorbing activities.

Conclusion: mAb and mAb-sCT conjugates were generated, purified and characterized. Conjugates retained high affinity and specificity for both RANK and sCT. Hence, this osteoclast targeting platform may prove of eventual utility in the therapeutic treatment of bone diseases.

25. Design and Development of a New Family of Self-assembling Gene Delivery Nanoparticles using Cationic Amino Acid Substituted Gemini Surfactants

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Purpose: A new family of amino acid substituted gemini surfactants was designed and synthesized to enhance gene delivery efficiency of self-assembling DNA nanoparticles.

Methods: Four new gemini surfactants were synthesized with the general chemical formula $C_{12}H_{25}(CH_3)_2N^+CH_2$-$CH_2$-N(AA)-$CH_2$-$CH_2$-$N^+(CH_3)_2$-$C_{12}H_{25}$ (AA= glycine, lysine, glycyl-lysine and lysyl-lysine). Nanoparticles were created by formulating plasmid DNA with substituted gemini surfactants in the presence of a helper lipid, dioleyl phosphatidyl ethanolamine. The complexes were transfected into rabbit epithelial cells. Protein expression (green fluorescent protein and interferon-γ) in the transfected cells was monitored by fluorescence microscopy and quantified by ELISA. The transfection efficiency of the substituted derivatives was compared to the unsubstituted gemini surfactant and a commercial agent. Cell toxicity of these gemini surfactants and DNA nanoparticles was determined by MTT assay. In addition, the nanoparticles were characterized using size and zeta potential measurements, transmission electron microscopy, circular dichroism and dye exclusion assays to determine how size, morphology, and DNA binding capability correlates with gene delivery efficiency.

Results: The study revealed a time-dependent increase in the gene expression for all the amino acid substituted cationic gemini surfactants. At all three time points tested (24 h, 48 h, 72 h), the novel compounds showed higher gene expression than the unmodified derivative, and their expression was comparable to Lipofectamine.

All gemini surfactants, in the absence of DNA and helper lipid, induced significant cell death; however, an overall low toxicity was observed for all DNA-gemini nanoparticles. Cell viability of glycine, lysine, glycyl-lysine functionalized nanoparticles was significantly higher compared to commercial Lipofectamine.

All the complexes formed nanoparticles in the size range of 100-150 nm, an optimum size for endocytosis. Net positive zeta potential (greater than +30 mV) contributed to colloidal stability and increased cell-nanoparticle interaction. Circular dichroism spectra of the complexes containing amino acid derivatives were similar to unsubstituted compounds suggesting no interference of amino acid substitution on DNA compaction. However, the dye exclusion assay suggested a more efficient protection of the DNA by the glycine and glycyl-lysine substituted compounds.

Conclusion: We developed a novel family of nanoparticle gene delivery systems that showed high transfection efficiency and low toxicity. The higher transfection efficiency of these complexes is attributed to better protection of DNA, biocompatibility and flexibility of the amino acid/peptide substituted gemini surfactants. Thus, this new family of gene carriers shows considerable potential for developing gene delivery systems that may help in treating diseases affecting epithelial tissue.

26. Micellar Paclitaxel and Docetaxel for Intravesical Bladder Cancer Therapy

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Purpose: Bladder cancer is the 6th leading cancer in Canada, and the majority of cases are superficial non-invasive cancers for which the standard treatment is transurethral resection (TUR). Intravesical chemotherapy is administered as an adjuvant therapy to TUR. Paclitaxel and docetaxel have demonstrated good activity against metastatic bladder cancer. While a few groups have demonstrated uptake of paclitaxel in the bladder wall, no studies have characterized the penetration and distribution of nanoparticulate formulations of docetaxel in bladder tissue.

Methods: Paclitaxel (1mg/mL) and docetaxel (5mg/mL, 1mg/mL and 0.5mg/mL) loaded methoxypolyethylene glycol-block-poly(D,L-lactic acid) micelles were prepared. Micelles were spiked with tritium labeled paclitaxel and docetaxel. Spiked Taxol® and Taxotere® were used as controls. Porcine bladder tissue pieces were exposed to drug solution, and drug concentrations were determined by liquid scintillation counting. Viability

of porcine bladder tissue was determined by conducting lactate dehydrogenase cytotoxicity assays. Tyrode buffer served as the assay media, and Triton X-100 (2%) was used as the high control. LDH release was measured by UV-Vis spectroscopy.

Results: The total bladder tissue concentrations of 1 mg/mL paclitaxel from MePEG-PDLLA and Taxol® were 16.9 μg/g and 7.3 μg/g, respectively. Bladder tissue treated with 1 mg/mL docetaxel from MePEG-PDLLA micelles displayed higher concentrations than tissue treated with Taxotere®. Tissue concentrations declined exponentially with respect to tissue depth. Approximately, 0.23% and 0.37% of the initial dose was recovered in bladder tissues treated with paclitaxel and docetaxel loaded MePEG-PDLLA micelles and 0.12% and 0.22% of the initial dose was recovered in bladder tissues treated with Taxol® and Taxotere®. Concentrations of docetaxel in bladder tissue following a 2 h incubation were greater than concentrations following a 1 h incubation. Pig bladder tissue was viable for many hours in the Franz diffusion cell as lactate dehydogenase levels remained relatively constant up to 8 hours after sacrifice.

Conclusion: Micellar formulations of MePEG-PDLLA may provide an improved method to deliver paclitaxel and docetaxel for intravesical therapy than their commercial formulations. Our model detected drug concentrations in tissue with good sensitivity and enabled experiments to be conducted during the course of the bladder tissue's viable time. Although docetaxel allowed for greater penetration than paclitaxel, micellar paclitaxel and docetaxel both showed higher tissue uptake levels compared to their respective commercial formulations. Taxanes represent a suitable family of drug candidates for intravesical bladder cancer therapy because of their high lipophilicity and tissue penetration characteristics.

27. Enhancement of Docetaxel Solubility via Conjugation of Formulation-Compatible moieties

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Purpose: This study pursues the chemical modification of DTX in order to improve the compatibility between the drug and the inner phase of a non-toxic nano-emulsion formulation.

Methods: Computer-based theoretical calculations were employed to direct the design of docetaxel (DTX) conjugates with enhanced solubility in the internal phase of a nano-emulsion formulation. The theoretically-identified optimal DTX conjugates were synthesized by direct attachment of lauroyl moieties through an ester linkage to DTX.

Results: In comparison to DTX, the conjugates exhibited significantly improved solubility in oil as predicted by our theoretical calculations. This contributed to high drug entrapment efficiencies (up to 97%) and a high drug loading capacity (5.7 % w/w) for the DTX conjugates. The mono-substitution of an acyl group at C-2' of DTX resulted in a conjugate with 37- to 46-fold lower cytotoxicity than that of the parent drug in two human cancer cell lines. The activity exerted by the mono-substituted DTX on the cancer cells was due in part to the cytotoxicity of the parent drug that was released via hydrolysis of the ester bond between the lauroyl moiety and the drug under biologically relevant conditions. In contrast, di- and tri-substitution of acyl groups at C-2', C-7 and/or C-10 of docetaxel resulted in non-hydrolysable conjugates which were found to be inactive.

Conclusion: Overall, our results show that computer-based theoretical calculation is a promising strategy for guiding the enhancement of material-drug compatibility in formulation development. As well, these studies confirm that chemical modification of docetaxel for enhancement of material-drug compatibility should be limited to mono-substitution at C-2' and result in a prodrug that is hydrolysable at a moderate rate under biologically relevant conditions.

28. Preparation and Performance of Spray Dried Propofol Formulation using pH-sensitive Polymeric Micelles

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Objectives: Propofol (PPF) is a well known intravenous anaesthetic. Recently, propofol has also shown benefit in the treatment of intractable migraine, nausea and vomiting particularly when associated with chemotherapeutic use. To be of value to such patients, therapies are best

administered orally in an out-patient setting preferably in tablet form; propofol, an oily liquid at room temperature, does not lend itself to such presentations. To address this issue we are developing a series of solid micellar formulations of propofol employing pH-sensitive poly(ethyleneglycol)-co-polymethacrylates (PEG-PMA) amphiphilic block copolymers to entrap and retain propofol during processing.

Methods: Three block copolymer candidates were screened for their ability to load PPF at a fixed drug loading level of 10% wt/wt. Formulations were prepared in a simple one-step process adding PPF with stirring to an aqueous solution of each polymer until clear solutions were obtained; these were then lyophilized to identify those of greatest propofol retention post drying. New preparations of the chosen formulations were then spray dried using lab-scale (Buchi) equipment fitted with a two-fluid nozzle and characterized. Lyophilized and spray dried formulations were re-suspended in phosphate buffer to determine; propofol recovery post drying; maximum aqueous solubility; micelle size (Malvern Zetasizer Nano); and solution stability (HPLC) at time of preparation and on stability. Caco-2 studies were performed with the selected spray-dried formulations to assess PPF release and translocation efficiencies. Diprivan (commercial oil in water emulsion) was used as a control.

Results: Block-copolymer candidates subjected to lyophilisation displayed PPF recoveries between 50% and 90%. When subjected to spray drying recoveries of up to 75% were recorded. Micelle size (c. 300 nm) and other characteristics (solution stability, maximum solubility) were similar post either lyophilisation or spray drying. Caco-2 studies demonstrated all micellar formulations achieved greater than 80% propofol translocation across the cell monolayer. No changes in assay, impurity levels or micelle size were noted after 3 months storage at 25^{o}C/60% RH.

Conclusions: Propofol mediated treatment of migraine, nausea and vomiting would be significantly more viable should simple oral solid dose formulations of the drug be made available. Here we have demonstrated that PPF, an oil at room temperature, can be readily formulated using novel block-copolymer micelles to generate stable free-flowing powders suitable for capsule or tablet administration; experiments to determine oral bioavailability in animals are planned to confirm in vitro results.

Clinical Sciences and Pharmacy Practice

29. New US-FDA Bioequivalence Approaches for Generic Drug Products

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Purpose: To describe current and proposed bioequivalence approaches for specific drug products.

Methods: Abbreviated New Drug Applications (ANDAs) for marketing new generic drugs in the United States (US) must be supported by studies showing bioequivalence (BE) between the generic and its corresponding reference. The determination of BE of some drug products has presented additional challenges to generic product approval. These drug products include highly variable drugs (HVDs) and multiphasic modified-release (MR) formulations. For HVDs, the Office of Generic Drugs (OGD) now accepts studies based on reference scaling average bioequivalence (ABE). A number of ANDAs using the reference-scaled ABE approach are under review at the OGD, and, to date, one drug product for which this approach was used is tentatively approved. Presently, the OGD is investigating the implementation of new BE metrics to ensure that generic versions of multiphasic MR formulations are therapeutically equivalent to (switchable with) their corresponding reference products.

Results: Lansoprazole and niacin/simvastatin are examples of HVDs for which the OGD has recommended the reference-scaled ABE approach for establishing BE. This approach adjusts the confidence interval acceptance criteria based on the variability of the reference product. The FDA has posted individual draft guidances on these drugs on its website. With respect to BE assessment for certain multiphasic MR formulations, the OGD considers that these basic formulations generally contain two different types of release mechanisms – such as an immediate-release (IR) portion and an extended-release (ER) portion. If IR portion of such

a formulation is necessary for rapid onset of activity, then it may be necessary to expect a partial AUC to also meet the 80-125% BE limits. This approach is illustrated by the zolpidem ER tablet guidance, also posted on the FDA website.

Conclusions: The Agency is proactively developing BE approaches for certain drug products and complex dosage forms. Thus, while the FDA's suggested alternative approaches may ease the regulatory burden for HVDs (which are thought to have a wide therapeutic index), it proposes additional BE acceptance criteria for complex dosage forms such as multiphasic MR formulations to assure equivalent performance between the generics and corresponding innovator counterparts.

30. Confounding in Pharmacoepidemiologic Studies of Fracture Risk

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Purpose: Pharmacoepidemiologic studies are essential in post-marketing surveillance to assess the real-world effects of pharmacotherapy. Results of studies that rely on healthcare utilization (administrative claims) databases, however, may be prone to residual confounding due to missing information. An independent risk factor for osteoporotic fracture is a confounder when its prevalence is imbalanced between drug exposure groups under comparison. If a confounding factor is not controlled for, its effect on fracture risk is falsely attributed to drug effects. Thus, better understanding of missing data that may lead to residual confounding will help assess the validity of pharmacoepidemiologic results. We therefore sought to identify major risk factors for fracture that are unmeasured in claims data.

Methods: We used MEDLINE literature, Statistics Canada documentation and results from an Ontario community study about osteoporosis to identify risk factors for osteoporotic fracture and their prevalence among female Ontario seniors. Risk factors were categorized as major or minor according to their strength of association with osteoporotic fracture based on estimates of relative risk (RR), and their prevalence among Ontario women aged 65 or more years. We focused on identifying major risk factors for osteoporotic fracture that are not captured by Ontario claims data.

Results: Low bone mineral density (T<-2.5; RR=2.6, prevalence=11%), prior adult fracture (RR=2.2, prevalence=25%), a marker of frailty/strength (use of arms to stand from a chair, RR=2.6, prevalence=41%), and history of falls (RR=1.8, prevalence=26%) were identified as major independent risk factors unmeasured in claims data. Although clinical fractures are available using claims data, most pharmacoepidemiologic studies only consider fractures within a 1-year lookback from treatment initiation. Failure to control for these four major risk factors may lead to biased results if imbalance exists between comparison drug exposure groups.

Conclusions: We identified four major independent risk factors for osteoporotic fracture unmeasured in claims data that are prevalent in female Ontario seniors. Controlling for these potential unmeasured confounders may strengthen the validity of estimated drug effects on fracture risk. Supplementing claims data with external data sources that contain these unmeasured risk factors is a promising method to adjust for residual confounding. Our results may also be useful in theoretical sensitivity analyses that consider the potential residual confounding effects of these unmeasured factors.

Pharmaceutical and Analytical Chemistry

31. Simultaneous Determination of Etoposide and its Cis Isomer in Rat Plasma by a Sensitive HPLC Method Using Monolithic Column

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Purpose: Etoposide is extensively used to treat both of solid tumors and hematological malignancies. Etoposide is a chiral drug and can be degraded form the active trans-isomeric form of the lactone to the inactive cis- isomer. Various HPLC methods for bioanalysis of drug and its cis isomer in human plasma have been reported. Most of these methods suffer from either large plasma sample volumes which make them inappropriate for animal studies or large volume of organic solvent for sample

preparation. In addition, most of these methods employ electrochemical or fluorometric detection. Therefore, the present study was aimed to develop a simple and sensitive HPLC assay for the quantitation of etoposide and its cis isomer in rat plasma using small volume of plasma and UV detection.
Methods: The analysis was carried out on a monolithic silica column, using a mixture of methanol, acetonitrile, phosphate buffer (0.020 M) containing 0.007% triethylamine (TEA); (18:19:63, v/v) adjusted to pH= 5.2 as mobile phase. The analytes were detected with UV detection at 240 nm. The sample preparation procedure involved simple, one step liquid extraction of analytes and internal standard (lamotrigine) from 100 µl plasma by 1 ml mixture of chloroform and n-hexane (80:20, v/v). Validation of the method was performed according to ICH guidelines. The presented method was successfully applied for the drug pharmacokinetic studies in rat.
Results: The chromatographic method resulted in well resolved and symmetrical peaks without interferences from endogenous plasma compounds. The retention times of internal standard, etoposide and cis isomer were 5.5, 8.25 and 9.7 min respectively. Analytical recoveries of etoposide and its cis isomer from plasma were greater than 91%. The calibration curves were linear over the concentration range of 20-1000 ng/ ml for etoposide and 50 - 500 ng/ ml for cis isomer when 0.1 ml aliquot of plasma was used. The assay enabled the measurement of etoposide and its cis isomer with a minimum quantification limit of 20 and 50 ng/ ml. The coefficients of variation for inter-day and intra-day assay were found to be less than 10% for both of etoposide and its cis isomer and accuracy ranged from 90 to 110%.
Conclusion: The simplicity and rapidness (one step extraction and 10 min run time), use of very low volume of both plasma (100 µl) and extraction solvent (1ml) and higher sensitivity are some of the advantages of the present method over the previously reported methods for analysis of etoposide and its cis isomer in plasma.

Natural Products

32. Analyzing the Potential Neuroprotective Effects of Native Newfoundland and Labrador Berries

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Purpose: Oxidative stress is believed to contribute to aging as well as damage during pathologies such as stroke and traumatic brain injury. Foods containing particularly high amounts of compounds such as antioxidants (e.g. polyphenols in blueberries) offer a potential means of protection against traumatic insults, as well as the normal aging process. In this project, extracts of native Newfoundland and Labrador bilberries were analyzed for neuroprotective effects against trauma and aging using cell cultures derived from brain tissue.
Methods: Primary cell cultures were produced from the cortex of neonatal rats and grown for up to 20 days *in vitro* (DIV). A well-described *in vitro* model of traumatic injury was used to produce linear mechanical strain (Ellis et al., 1995). Two different injury levels of 5.5 mm and 6.5 mm deformation were utilized. Cell health was monitored in the presence of bilberry extracts, in comparison to non-treated cells. The number of neurons and glia were determined using immunohistochemistry techniques. Lactate and pyruvate were measured in cell culture media using a multi-assay biochemical analyzer.
Results: Aging experiments showed that up to 17 DIV cultures demonstrated no significant death of neurons, however by day 20 there was dramatic neuronal loss. For glial cells, proliferation was observed by day 17. No noticeable effect was shown on the glia and neurons with the addition of the extracts in the aging model. Significant neuronal loss was evident following 6.5 mm injury, but not after 5.5 mm injury. High levels of lactate were measured after injury, indicating that cells were unhealthy. Extracts were added to cultures 15 min before injury; lactate levels dropped significantly in both 5.5 mm and 6.5 mm injury in the presence of extracts.
Conclusion: The trauma model showed death in both glial cells and neurons as previously reported (e.g. Engel *et al*., 2005). A cell culture aging effect

was also observed. However, there was no noticeable effect on neurons and glia numbers after injury with the addition of bilberry extracts. There was a significant effect on lactate levels after injury in the presence of extracts, suggesting some beneficial effects of bilberry extracts in protecting against traumatic injury.

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33. Natural Health Product and Traditional Medicine Effect on the Activity of Human Hepatic Microsomal-mediated Metabolism of Oseltamivir

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Purpose: Oseltamivir is a prodrug that requires metabolic activation but there is little information on whether Cree traditional medicinal botanicals and other natural health products interact to prevent the biotransformation by the carboxylesterase.

Methods: HPLC-DAD-ESI-MSD and fluorometric assays were used to determine if 50-pooled mixed gender human liver microsomes can mediate the formation of the active carboxylate metabolite and then if this reaction is affected by natural health products.

Results: Extracts from 6 traditional Cree botanicals, a commercially available Echinacea product, Goldenseal and a traditional Chinese medicine reduced the formation of the active drug. In addition to oseltamivir carboxylate we report the detection of two new metabolites which are derivatives of oseltamivir carboxylate, one of which is a metabonate formed as a result of methanol.

Conclusions - Implications: *In vitro* studies would suggest that there is the potential for some natural health products used by patients in response to pandemic A/H1N1 to reduce drug efficacy. Further studies are required to determine if these potential interactions could be clinically significant. There is limited information available on whether natural health products (NHPs) that may be used concomitantly with oseltamivir will affect the safety and efficacy of this drug. This is the first study to examine whether some traditional medicines used by the Cree in Canada, and other NHPs, traditional Chinese medicines may result in a potential interaction that will reduce the efficacy of this drug. Clinical investigation to determine the significance of this finding is warranted.

Pharmacokinetics and Pharmacodynamics

34. Effect of Diltiazem on RBC Concentrations of Adenine Nucleotides in Zebrafish and Restraining Rat Model *in vivo*

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Purpose: To study the effect of diltiazem (DTZ) on the RBC concentrations of ATP and purine nucleotides using a zebrafish and rat model *in vivo*.

Methods: Zebrafish (*Danio rerio*) weighing approximately 0.3 g and male rats (SD and SHR between 250 and 300g) were used. The zebrafish received saline (n = 20) or DTZ (15 mg/kg) (n = 6) twice daily by intra-peritoneal injection for 3 doses. Each rat received saline (n=15) or DTZ (5 mg/kg, n = 9) twice daily by subcutaneous (sc) injection for 5 doses. Blood samples were collected from each zebrafish one hr after the last injection, and from each rat serially for up to 6 hrs while the rats were kept in a restrainer. Concentrations of ATP and other purine nucleotides in RBC lysates were determined by a validated HPLC assay. Data were corrected for dilution and normalized for hematocrit value. Differences between groups were evaluated by ANOVA and considered significant when $p < 0.05$.

Results: RBC concentrations of ATP, ADP and AMP were significantly higher in the SHR than the SD rats and the zebrafish ($p<0.05$). DTZ increased RBC concentrations of the adenine nucleotides in the zebrafish, but not in the restraining rat model. The species difference of the pharmacologic effect

could be related to the higher dosage (15 mg/kg vs 5 mg/kg) and freely moving environment inherent in the zebrafish model.

Conclusion: The RBC concentrations of adenine nucleotides are useful biomarkers in the zebrafish and rat model which may be applied in tandem for evaluation of cardiovascular drugs (Supported in part by CIHR, Nova Scotia Health Research Foundation and Dalhousie Pharmacy Endowment Foundation).

Table 1. RBC Adenine Nucleotide Concentrations[a]

Purine Nucleotides	Zebrafish	
	Control	DTZ
ATP (mM)**	0.40±0.18	0.75±0.24*
ADP (mM)**	0.14±0.071	0.32±0.10*
AMP (mM)**	0.047±0.026	0.092±0.047*
Purine Nucleotides	**SD Rats**	
	Control	DTZ
ATP (mM)**	1.26±0.34	1.26±0.56
ADP (mM)**	0.53±0.16	0.70±0.34
AMP (mM)**	0.15±0.18	0.21±0.22
Purine Nucleotides	**SHR**	
	Control	DTZ
ATP (mM)**	2.05±0.91	1.78±0.67
ADP (mM)**	0.89±0.59	0.92±0.46
AMP (mM)**	0.34±0.16	0.39±0.37

[a] Concentration determined from blood sample collected 1 hr after the last injection for zebrafish, and average concentration over 6 hrs for rats.
Values are mean ± SD.
*p<0.05 from control
**p<0.05 for species difference

35. Pharmacokinetics, Pharmacodynamics and Assay Development of 3'-hydroxypterostilbene

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Purpose: To develop a method using RP-HPLC to quantify 3'-hydroxypterostilbene; characterize the pharmacokinetics of 3'-hydroxypterostilbene in rats after intravenous (IV) and oral (PO) administration; and identify pharmacological activity of 3'-hydroxypterostilbene.

Methods: In the developed assay, the stationary phase consisted of a Phenomenex® Luna® $C_{18}(2)$ column with UV detection at 325 nm. The mobile phase consisted of acetonitrile, water, and formic acid (50:50:0.01, v/v/v/), at a flow rate of 0.8 mL/min. Linear standard curves were established and the assay applied in a pharmacokinetic study. Male Sprague-Dawley rats were either IV or PO dosed (10-100 mg/kg) with 3'-hydroxypterostilbene; urine, serum, and fecal samples were collected for 120h post-dose. *In vitro* cell proliferation, anti-oxidant, and anti-adipogenic activity, cyclooxygenase (COX)-1 and -2 inhibitory activity, histone deacetylase (HDAC), sirtinol 1 (SIRT1), and P-glycoprotein modulation was examined using ELISA over the concentration range of 0-250 µg/mL. Male NIH Swiss mice were subjected to the hot plate and tail flick tests to examine nociception after an intraperitoneal administration of 3'-hydroxypterostilbene (50 mg/kg).

Results: A developed and validated method for the 3'-hydroxypterostilbene was utilized to assay biological matrices including urine, plasma and feces. The precision and accuracy of this method was validated with intra-day and inter-day assay conditions, recovery, and stability, following and within acceptable International Conference on Harmonization guidelines. The method detected 3'-hydroxypterostilbene in urine primarily as the glucuronide, while in serum and fecal samples primarily as the aglycone. Pharmacokinetic parameters were delineated and bioavailability substantially reduced while F_e was relatively unchanged after PO administration. Pharmacodynamic data suggests that 3'-

hydroxyptersotilbene possesses anti-oxidant and anti-adipogenic activity, is a COX-1 and -2, HDAC, and SIRT1 inhibitor, and modulates P-glycoprotein but has minimal anti-proliferative activity.

Conclusions: A sensitive, reproducible, and accurate assay was developed for the detection of 3'-hydroxypterostilbene using RP-HPLC. Preliminary pharmacokinetic data indicated that 3'-hydroxypterostilbene is extensively metabolized and excreted in urine as its glucuronide. 3'-hydroxypterostilbene exhibits a variety of pharmacological activities *in vitro* and anti-nociceptive activity *in vivo*.

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36. The Effect of Increased Lipoprotein Levels on the Pharmacokinetics of Ketoconazole Enantiomers in Rat

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Purpose: We have found that in hyperlipidemic (HL) plasma of poloxamer (P407) treated rats, there was a shift of ketoconazole (KTZ) enantiomers to plasma lipoproteins. Here we examined the effect of experimental HL on the pharmacokinetics of KTZ enantiomers.

Methods: Sprague-Dawley rats were allocated into either normolipidemic (NL) or HL groups. KTZ was administered as 10 mg/kg iv or 40 mg/kg orally. Serial blood samples were collected over a 24 h period via surgically-implanted right jugular vein cannulas for the iv dosed groups. After the oral dosing, rats were anaesthetized and plasma and liver specimens were obtained at 0.5, 1, 1.5, 3, 6 h post dose. Plasma and liver were assayed for KTZ enantiomer concentrations using a stereospecific assay.

Results: Both orally and iv dosed rats showed no significant differences between NL and HL area under the plasma concentrations vs. time curves (AUC) or clearance (CL) of either KTZ enantiomer. In iv dosed rats, however, volume of distribution (Vdss) was significantly increased in HL for both KTZ enantiomers. Half life showed no difference between NL and HL rats. The ratio of KTZ of plasma AUC decreased, while that of clearance and Vdss increased significantly in HL rats. In orally dosed rats, the liver and KTZ $AUC_{0\text{-}6h}$ were significantly lower in HL than in NL rats. The liver to plasma concentration ratio for the KTZ enantiomer was also significantly lower in HL.

Conclusion: HL caused no change in most of KTZ pharmacokinetic parameters except for an increase in Vss. It also resulted in different enantiomeric pharmacokinetic ratios and lower liver concentrations. The increase in Vdss may reflect an increased lipoprotein-mediated transport of the drug to extrahepatic tissues. Funding in part by CIHR MOP 87395.

37. Glucosamine Prevents Adjuvant Arthritis and Restores Diminished Response to Verapamil Caused by Inflammation

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Purpose: Glucosamine (GlcN) is a naturally occurring amino sugar, which is believed to have the property to slow down and probably reverse inflammatory process. Using a rat model of adjuvant arthritis (AA), we investigated the role of GlcN in restoring the reduced response to verapamil in presence of inflammation. In addition, the effect of GlcN on the development of arthritis was investigated.

Methods: Adult male Sprague-Dawley rats were randomly assigned to six groups (n=6): inflamed-prevention, inflamed-Treated (continued & discontinued), Inflamed-placebo, Control-GlcN, and Control-placebo. On day zero, 0.2 ml Mycobacterium Butyricum in Squalene (50 mg/mL) or saline was injected to the inflamed and control groups, respectively. The prevention groups were administered GlcN hydrochloride (300 mg/kg/day, p.o. commenced on day zero), while the control groups received saline. The treated groups received GlcN upon developing the early sign of AA; after amelioration of the disease, the GlcN administration continued in the "Continued group", whereas stopped in the "discontinued group. On day 14 (for control and prevention groups) and day 18 (for treated groups), ECG leads were implanted S.C., a single oral dose of 25 mg/kg verapamil administered, and PR interval measured in certain time points. On day 17 (for control and prevention groups) and day 21 (for treated groups), animals were cannulated in the jugular vein and after recovery, the same verapamil dose administered again and serial blood samples collected. Blood samples were analyzed for verapamil using HPLC.

Plasma Nitric oxide (NO) concentration was assessed indirectly by measuring the concentrations of its stable products nitrite and nitrate. Utilizing western blotting, protein contents of L-type calcium channel, beta 1-adrenoreceptors and ryanodine-2 receptor were measured. During the experiment, animal's paw diameter and weight were monitored.

Results: All rats that received Mycobacterium butyricum but were not treated with GlcN, developed arthritis. GlcN treatment completely prevented arthritis. Inflamed-placebo rats had up to 3-fold greater plasma verapamil concentration and demonstrated reduced response to verapamil in terms of PR prolongation. Prevention or continued treatment with GlcN of the inflamed rats resulted in restoration of response to verapamil. Normalization of the increased verapamil concentrations was observed only in prevention group but not the treated groups. The expression of calcium channels and Beta 1-adrenoreceptors in inflamed groups were down regulated and were normalized after GlcN administration. However the expressions of these proteins in prevented groups were not significantly altered comparing to control groups. No significant alteration was observed in ryanodine receptor expression in control, prevention, and treated groups. Serum nitrite concentration was significantly elevated by inflammation and was normalized by GlcN treatment.

Conclusion: Present data confirm that GlcN prevent adjuvant arthritis and restores down-regulation of calcium channel receptors.

38. Metabolite Disposition of the Repellent DEET and the Sunscreen Oxybenzone in Rats

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Purpose: Concurrent application of the repellent DEET and the sunscreen oxybenzone (OBZ) enhances the disposition of the two compounds *in vivo*. This study investigated the metabolism of DEET and OBZ in a rat model.

Methods: DEET and OBZ were topically applied to male Sprague-Dawley rats, either alone (S) or in combination (C), for 24 hours. Blood, urine, and feces samples were collected at different intervals for 24 hours. Livers and kidneys were harvested at the end of the study. HPLC analysis identified N, N-diethyl-m-hydroxymethylbenzamide (DHMB) and N-ethyl-m-toluamide (ET) as the major DEET metabolites, and 2,4-dihydroxybenzophenone (DHB), 2,2´-dihydroxy-4-methoxybenzophenone (DHMB), and 2,3,4-trihydroxy-benzophenone (THB) as the main OBZ metabolites.

Results: DEET metabolites were detected in all samples collected. DHMB was the major metabolite in urine and feces with combined application (6.33±0.05 μg/mL and 2.11±0.18 μg/g, respectively) exceeding single application (5.87±0.04 μg/mL and 1.78±0.20 μg/g, respectively). The liver contained the highest amount of DEET metabolites per gram of tissue (91.7±1.4 ng/g for C vs. 65.0±3.2 ng/g for S). THB was the main OBZ by-product detected in tissues (619.6±11.1 ng/g for C vs. 545.6±12.7 ng/g for S), but was not found in the feces or plasma. The kidney contained the highest amount of OBZ metabolites per gram of tissue (473.8±6.2 ng/g for C vs. 439.9±7.3 ng/g for S). Urine was the primary route of excretion for all metabolites. Significant differences between the two applications were found for DHMB, ET, DHB and THB in liver, kidney and urine, for DHB and DMB in feces, and for DMB in urine (Mean±SEM, n=5, $p<0.05$).

Conclusion: DEET and OBZ were extensively distributed and eliminated following topical skin administration in rats. Combined application of DEET and OBZ enhanced the disposition of all metabolites *in vivo*.

AFPC
Poster Presentations
Day 1
Thursday, June 3, 2010

Day 1

Basic Science

39. Optimization of Nasal Tissue Culture Conditions for SLC Transporters Gene Expression

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Background: Human nasal tissue monolayer culture system has become an important tool in the study of drug delivery via nasal route, but the variance of cell culture conditions in different laboratories makes it difficult to compare and interpret experimental results.
Objectives: The aim of this study was to test the effect of common culture conditions on gene expression of major SLC drug transporters (peptide, organic cations) in human nasal epithelium.
Methods: Human nasal epithelia were collected from patients undergoing nasal reconstruction for sleep apnea. The specimens were dissociated enzymatically using 1.0% protease XIV. The harvested cells were then cultured in 35x10 mm polystyrene culture dishes. The following conditions were tested - binding surfaces: plastic only, rat tail collagen film, and rat tail collagen gel; media: DMEM F12 with 2% Ultoser G, with 10% FBS, and with 10% Nu serum; culture duration: 1, 2, 4 weeks. The effect of passaging was also tested. Cells were subjected to trizol extraction and cDNA synthesis. Gene expression of SLC transporters (OCT1, OCT2, OCT3, OCTN1, OCTN2, PEPT1, PEPT2, PHT1, PHT2) were detected by qPCR.
Results: Culture media had a major effect on gene expression levels as follows: Ultoser G > FBS > Nu serum. Binding surface had less or no effect on gene expression. The expression of the genes increased with culture time and passaging had no effect.
Conclusions: Ultroser was identified as the most efficient culture supplement in maintaining SLC transporter gene expression, whereas FBS appears to be an economical choice. Nu serum is not suggested. Plastic is suitable for nasal tissue culture since coating doesn't change the gene expression significantly.

40. Local Anesthetic-like and N-Methyl-D-Asparatate (NMDA) Receptor Blocking Effects of Intramuscularly Injected Ketorolac

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Objectives: It is generally accepted that the analgesic effect of non-steroidal anti-inflammatory drugs, such as ketorolac, is derived from the ability of NSAIDs to decrease the synthesis of pro-inflammatory prostaglandins through inhibition of the enzyme cyclooxygenase (COX) to exert a local inhibitory action on nociceptive afferent fibers (nociceptors). However, intramuscular injection of ketorolac results in local tissue concentrations that greatly exceed those required to inhibit COX, which may mean that additional mechanisms contribute to its analgesic actions. The present study was undertaken to investigate whether intramuscular injection of ketorolac could attenuate jaw-closer muscle nociceptor discharge through a local anesthetic-like effect.
Methods: Putative muscle nociceptors were recorded in the rat trigeminal ganglion and identified by their response to mechanical stimulation of the masticatory muscle and projection to the caudal brainstem. To assess for possible local anesthetic-like effects of ketorolac on nociceptor discharge, an initial intramuscular injection of hypertonic saline was followed 30 min later by a second injection of hypertonic saline alone (control, n=8), with lidocaine 2% (positive control, n=8), or with ketorolac (0.13% or 0.013%, n=4 each). To examine ketorolac's effect on peripheral NMDA receptors, an initial intramuscular injection of NMDA was followed 30 min later by a second injection of NMDA (control, n=8) alone, or with ketorolac (0.013%, n=3). The second response was divided by the first to yield relative nociceptor discharge.
Results: Compared with injections of hypertonic saline alone, co-injection of either 0.13%, but not 0.013% ketorolac or lidocaine with hypertonic saline significantly decreased relative nociceptor discharge.

Compared with injections of NMDA alone, co-injection of 0.013% ketorolac with NMDA decreased relative nociceptor discharge.
Conclusions: Ketorolac exerts local anesthetic-like actions at a concentration of 0.13% (5 mM). At one tenth this concentration, ketorolac is without local anesthetic-like actions, but is capable of inhibiting peripheral NMDA receptors. These findings indicate that mechanisms other than COX inhibition may contribute to the local analgesic effect of intramuscularly injected ketorolac.

41. Protein Arginine *N*-Methyltransferase Inhibitors Bearing an N^G-modified L-Arginine Residue

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Background: Protein arginine *N*-methyltransferases (PRMTs) are eukaryotic enzymes that use *S*-adenosyl-L-methionine (AdoMet) to methylate arginine residues in proteins, and also form *S*-adenosyl-L-methionine (AdoHcy). PRMT activity is involved in controlling many cellular pathways including gene expression, and these enzymes are currently considered potential therapeutic targets for the treatment of cancer and other diseases. Whereas existing PRMT inhibitors target the AdoMet binding site common to many methyltransferases, we have developed arginine derivatives that resemble the PRMT intermediate product N^G-monomethylarginine.
Methods: We synthesized a series of peptides: WGGYSR^{X}GGYGGW where R^X is arginine, N^G-monomethylarginine (MMA), asymmetric N^G,N^G-dimethylarginine (aDMA), symmetric N^G,N'^G-dimethylarginine (sDMA), N^G-ethyl- (EtArg), N^G-fluoroethyl- (FEtArg), N^G-difluorethyl- (F_2EtArg), or N^G-trifluoroethylarginine (F_3EtArg). Using ultra-performance liquid chromatography tandem mass spectrometry to measure PRMT activity, we are able to determine if these peptides are PRMT substrates or inhibitors.
Results: PRMT1 methylates the peptide bearing EtArg on the substituted nitrogen atom, confirming that its active site can accommodate the substitution. However, introducing fluorine atoms on the ethyl substituent eliminates methylation of the arginine residue, and inhibits methylation of other substrates. We have determined that the PRMT1 IC_{50} for F_3EtArg is 13.9 ± 1.8 μM, which is 2.5-fold lower than for EtArg, 5-fold lower than for the product inhibitor aDMA, and 24-fold lower than for sDMA. *Ab initio* calculations of arginine and its derivatives indicate that while partial charges of guanidino nitrogen atoms appear unaffected by added substituents, the guanidino dipole moment changes orientation and magnitude with an increase in the number of fluorine atoms, suggesting that fluorinated substituents alter the electronic properties of the guanidino group so that methyl transfer onto the nitrogen atom is prevented.
Conclusions: The results of this study demonstrate that fluoroethyl-substituted arginine peptides represent lead compounds for the further development of PRMT-selective inhibitors.

42. Characterization of organic cation transporters in human bronchial cell line (Calu-3)

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Background: The Calu-3 cell culture model is well characterized for drug permeation and metabolism studies. However, the available literature information is limited to compounds that permeate the cells by passive diffusion.
Objectives: The objective of this study was to characterize the expression of active transport systems for organic cations in Calu-3 cells.
Methods: Drug uptake, inhibition and transport studies were performed using a published fluorescent organic cation 4-dimethylaminostyryl-N-methylpyridinium (4-Di-1-ASP). Expression profiling of the transporters was determined using quantitative polymerase chain reaction (qPCR), western blotting and immunohistochemistry.
Results: The uptake 4-Di-1-ASP in Calu-3 cells was concentration, temperature, and pH dependent. L-carnitine and quinine almost completely inhibited the active transport component of 4-Di-1-ASP

uptake. MPP+, TEA and D-carnitine showed slight inhibition. The optimal pH range for the uptake was 7.4 - 8.5. Organic cation transporters OCT1, OCT3, OCTN1 and OCTN2 were confirmed to be expressed in the cell line with OCTN2 showing the most significant gene expression.
Conclusions: This work showed that the Calu-3 cells functionally express organic cation transporters. Utilizing these uptake transporters in the respiratory epithelium can provide a means to improve absorption of topically applied drugs to treat respiratory tract diseases and for systemic drug delivery.

43. GPR103b, a New G Protein-coupled Receptor, Mediates the RFamide Peptides QRFPs Regulation of Peripheral Adipogenesis

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The RFamide peptides QRFPs have been recently identified as endogenous ligands of the orphan G protein-coupled receptors GPR103a and b, expressed in hypothalamic regions important in appetite regulation. Intracerebroventricular injection of QRFPs induced hyperphagia, leading to an increase in body weight and fat mass. However, the role for the GPR103/QRFP system in peripheral lipid homeostasis has not yet been investigated.
Objectives: 1) to document the expression of GPR103 in primary mice adipocytes and 3T3-L1 cells during their differentiation to mature adipocytes; 2) to characterize the role of GPR103 in QRFP-elicited fatty acid uptake and lypolysis inhibition; 3) To assess the role of GPR103 in mediating QRFPs regulation of adipogenesis.
Results: The GPR103b receptor subtype was selectively expressed in 3T3-L1 adipocytes during differentiation, in a time-dependent manner. Low levels of QRFP mRNA were detected in 3T3-L1 pre-adipocytes, which increased by 5-fold ($P < 0.05$) 4 days after the induction of cell differentiation. QRFP-43 and -26 (10 nM) treatment induced a 27 ± 3 and 31 ± 2% ($P < 0.05$) increase in FA uptake compared to vehicle, respectively. Specific GPR103b knockdown abolished QRFP-mediated FA uptake. QRFP-43 nor QRFP-26, feature antilipolytic effects on isoproterenol-induced lipolysis with IC50s of 2.3 ± 1.2 and 1.1 ± 1.0 nM, respectively, which were abolished following GPR103b knock down in differentiated 3T3-L1 cells. GPR103b appears to mediate the effect of QRFPs peptides by promoting the expression of adipogenic genes (PPARγ-C/EBPα, FATP1, ACSL1) in differentiated adipocytes expressing this receptor.
Conclusion: In addition to the central regulation of energy homeostasis, GPR103b is involved in the regulation of peripheral adipogenesis in response to QRFP peptides suggesting GPR103b as a potential target in the treatment of obesity.
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44. A New Approach to Improve Survival of Human Islets during Pre-Transplant Culture

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Background: Type 1 diabetes (T1D) is characterized by destruction of pancreatic beta-cells and hyperglycemia which leads to life-time insulin therapy. Human islet transplantation is a promising approach for treatment of T1D but is currently limited by loss of islets during pre-transplant culture and following transplantation. Exenatide is a long acting analogue of glucagon-like peptide-1 that has been approved as an anti-diabetic drug for treatment of T2D.
Objectives: In this study, we examined whether exenatide treatment could reduce beta-cell death and improve survival of human islets during pre-transplant culture as a potential approach to increase the yield of islets isolated from pancreatic donors.
Methods: Freshly isolated human islets from cadaveric donors were cultured for 7 days in the presence or absence of exenatide. Cultured islets were fixed in paraformaldehyde and paraffin-embedded islet sections were used for immuno-histochemistry studies.
Results: Culture of human islets resulted in beta-cell death leading to a decrease in the islet beta/alpha cell ratio during culture (d0: 1.7 ± 0.3 vs. d7: 1.3 ± 0.2, $P<0.05$) and an increase in the proportion of apoptotic (TUNEL-positive) islet cells (d0: 3.4 ± 1.2% vs d7: 12.1 ± 2.4%, $P<0.05$). Treatment with exenatide resulted in an increase in the islet beta/alpha cell ratio (+Ex: 1.6 ± 0.2%, $P<0.05$), intensity of insulin immunostaining and a decrease

in the proportion of TUNEL-positive islet cells (+Ex: 7.3 ± 1.4%, P<0.05). Double insulin/TUNEL staining showed that the majority of TUNEL-positive cells were beta cells. This decrease in the number of TUNEL-positive beta cells in exenatide-treated islets was associated with a marked decrease in caspase-3 activation as assessed by double insulin/active caspase-3 immunostaining.
Conclusions: These findings suggest that treatment with exenatide reduces beta-cell apoptosis and decreases caspase-3 activation in isolated human islets during culture. Exenatide treatment provides a new approach to restore islet mass during pre-transplant culture and increases the success rate of clinical islet transplantation.

Education and Teaching Research

45. Development of an Oral Examination in a Pharmacotherapeutics Course for a Large Class

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Background: The Pharmacotherapeutics course is taught in a large class of 240 students. An oral examination (OE) was identified as one way to effectively assess students' ability to identify and resolve drug therapy problems. Previously, a group OE (testing 10 students together) was implemented; however an accurate assessment of each student's ability was identified as a challenge.
Objective: To develop tools and format for the administration and evaluation of a one-on-one OE in a Pharmacotherapeutics for 240 students.
Methods: Based on previous experience, a determination was made on the number of cases needed to test each student. An initial modeling was done using Excel to establish the number of examiners and rooms required. Evaluation criteria were determined in consultation with an assessment expert. Exam case developers were identified and potential schedules were developed. A mock exam was done with 25 instructors to test for case validity and reliability. All examiners were trained during a workshop and an exam review session was held for students to discuss the exam and evaluation process. Post-OE feedback was obtained from students and examiners.
Results: Each student undertook 3 OE based on 3 paper patient cases (total 720 exam sessions) over one day. Thirty examiners were trained and the exam took place in 30 rooms. Each exam case took 30 minutes per student to complete. Feedback indicated that the cases and the process worked well and this OE enabled a more accurate assessment of students' knowledge and skills. Evaluation tools and cases will be shared.
Conclusions: Students, examiners and course coordinators indicated that this was an effective way of examining students' therapeutic knowledge and skills. The process was refined and the exam was offered in another course. This exam continues to be an important evaluation tool in the Therapeutics courses.

46. Reinforcing Professionalism in Pharmacy Students Beginning Senior Experiential Rotations

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Objective: Structured Practical Experiential Program (SPEP) faculty (University of Toronto) responded to an identified need to reinforce knowledge, skills and values related to professional behaviour (PB) and ethical responsibility (ER). The design, implementation and results of small group PB and ER tutorials are described.
Methods: Mandatory interactive 2-hour tutorials of approximately 20 students led by SPEP faculty and preceptors were conducted in November, 2009. The lesson plan consisted of: pre-readings (including: Pledge of Professionalism, OCP Code of Ethics, textbook chapter); discussion; break-out groups examining controversial scenarios; and feedback. Participation was documented and thoughtfulness in responses was expected. Students submitted requisite post-tutorial personal reflections related to PB and ER. If these submissions indicated weak understanding or poor insight a re-submission was required. Effectiveness was measured through tutorial evaluations, performance during rotations (PB assessment forms) and a preceptor survey.
Results: Two hundred and thirty students completed the tutorial evaluation form. The responses were positive in terms of organization of the sessions and

relevancy of the topics. Ninety-two percent (92%) of the respondents selected 'agree' or 'strongly agree' that 'the material is relevant to my Pharmacy education'. An even higher percentage of respondents (97%) indicated agreement or strong agreement that 'the material is relevant to a future career as a pharmacist'. Preceptor PB assessments from January/February 2009 rotations indicated 9 instances of sub-par student performance versus 10 in 2010. However, no egregious incidents were reported in 2010 which was not the case in 2009. TA survey results are pending.

Conclusion: Perceived utility of the tutorial by students and Faculty merits consideration for retaining the PB and ER tutorial. Student performance as measured through the PB form showed a minimal difference between 2009 and 2010. This finding warrants further investigation of confounding factors.

47. Effective Delivery of an Interprofessional Problem-based Learning Module to Health and Human Service Students at the University of British Columbia

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Objectives: Problem-based learning (PBL) has been recognized as a strategy to maximize the effectiveness of interprofessional learning. This project expands on an interprofessional problem-based learning (IP-PBL) pilot project that was presented at *Collaborating Across Borders II*. The aim of the second phase of this project was to build on the lessons learned from the first pilot of the module by:

- Modifying the case about a mother with post-partum depression and low back pain, to make the interprofessional learning more explicit;
- Developing and implementing a facilitator training strategy in order to prepare facilitators for the unique experience of facilitating PBL using an interprofessional approach;
- Exposing a larger group of students from medicine, pharmacy, nursing, physical therapy and occupational therapy to the refined module; and
- Evaluating the new module.

Methods: Seventy-seven students from the disciplines listed above were exposed to the module in groups of six to seven during two 2-hour sessions spaced one week apart. A faculty member who had received training through a 3-hour workshop facilitated each group. Using pre- and post-questionnaires, the module was evaluated for its impact on students' interprofessional knowledge, skills and attitudes, as well as for ease of implementation.

Results: The IP-PBL module, implementation plan, evaluation tools, and evaluation data will be presented.

Conclusions: This project indicates that PBL, undertaken with an interprofessional group of students, is an education strategy that has the ability to enhance students' knowledge, teamwork skills, and understanding of other professions' roles. The ease of implementation into a large educational institution remains a major challenge.

48. Pilot Test of Multiple Mini Interviews as an Admissions Tool for a Pharmacy Degree Program

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Objectives: The Multiple Mini Interview (MMI) is an admissions interview system, developed at McMaster University School of Medicine, which structurally resembles the OSCE. This study assessed the feasibility and discriminant validity of an MMI modified for pharmacy, and determined optimal station length.

Methods: A 10-station MMI covering 8 non-cognitive attributes was adapted from McMaster's MMI (ProFit HR®). Stations were either 8 or 6 minutes with 2 minutes in between. Candidates were recruited from the incoming pharmacy class. Faculty, practitioner and student (years 2-4) interviewers received 2 hours of training. Performance at each station was rated on a 10-point scale and station ratings summed. Candidates and interviewers provided feedback on structured questionnaires and in group debriefings. Descriptive statistics were calculated for quantitative responses on questionnaires and for MMI scores. Qualitative data were content analyzed. Pearson r correlation coefficients were calculated between MMI score, pre-pharmacy GPA and PCAT scores.

Results: Of the 30 candidates, 63% were female and 63% had 1-2 prior years in university, versus 55% and 45% respectively in the full class. Student interviewers (n= 8) rated candidates slightly higher (6.0 +/- 2.5) than faculty (n=7) (5.5 +/- 2.2) or practitioners (n=15) (5.4 +/- 2.5). Interview scores ranged from 26 to 79 out of 100. Correlation of the MMI score with GPA was -0.025 and with PCAT composite 0.042. Most interviewers (69%) judged a 6-minute interview 'just right' and 8 minutes 'a bit long'; 47% of candidates found 6 minutes 'just right' or 'a bit short' (50%) and 8 minutes 'just right' (50%) or a 'bit long' (43%). Station scenarios had face validity for both candidates and interviewers. Overall, participants were enthusiastic about the MMI process and experience.
Conclusions: The pilot test confirmed the feasibility of the MMI. For 2010, station length will be 7 minutes; student interviewers will be from years 3 and 4 only. Low correlations indicate that the MMI measured different attributes than the PCAT and GPA.

49. Demonstration Project to build Practice Education in Residential Care (RC) Facilities in British Columbia

Rosemin Kassam, Mona Kwong, *Angela Kim-Sing*. Faculty of Pharmaceutical Sciences, University of British Columbia

Objectives: 1) To develop practice education opportunities for pharmacy students within RC facilities; 2) To develop an educational module and syllabus to support preceptor and student learning; 3) To identify the learning activities and skill development opportunities; 4) To identify challenges to the implementation.
Methods: In BC the RC facilities are primarily serviced by community pharmacy with a limited number serviced by hospital pharmacies. Two community and two hospital sites were selected to participate in the project. The project was carried out in two phases between August 2006 and August 2007. An educational module "Care for the Elderly" was used to assist participating students and preceptors in enhancing their knowledge, skills and attitudes. A three-day workshop was delivered to ensure the students had the baseline knowledge in select chronic diseases of the elderly. A syllabus with specific expectations was developed. Surveys were conducted to evaluate the student's opportunities and learning experiences.
Results: The project was successful on many fronts. In the initial two phases a total of eight student placements in RC were created. Overall the students felt that the RC facilities provided them with sufficient opportunities to meet most of the learning objectives of the practice education program. Challenges to the project included minimal face-to-face preceptor to student interaction. The technology to support interactions was further limited by firewalls, IT departments and preceptor inexperience.
Conclusions: Through this project we were able to expand capacity in the experiential learning program to include RC facilities. Placement capacity in RC went from zero to eight placements in the initial phase, to over 35+ placements available to our current students. With the "Care for the Elderly" Module, SPEP faculty has delivered training to over 70 preceptors. The next step is to continue with the current initiatives to ensure successful and sustainable development of the RC sites, to further enhance the experience and continue to expand capacity.

50. The Virtual Classroom - Linking Experiential Education across Alberta

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Objectives: Rural pharmacy placements are an important component of the experiential education program in Alberta. However, placements located outside of Edmonton and Calgary can present challenges to students by way of their geographical location. Virtual classrooms were created to promote and enhance student experiences.
Methods: One of the key components of the virtual classroom is communication. Experiential education coordinators across the province designed and implemented a web based virtual classroom as a mechanism to explore and formalize a learning partnership with students and preceptors. Elluminate®, and Blackboard® were the primary communication technologies used.
Results: Teams of three to four students and a regional faculty member met weekly or biweekly on e-class using the Elluminate® platform. Activities included presentation of patient care experiences, learning projects, journal club, peer assisted documentation assignments and reflective learning blogs. Preceptors posted questions in discussion

boards and shared resources on e-class. Use of similar technologies between medical and pharmacy students provided opportunities for collaborative patient care and joint reporting of patient care experiences. A community health module was introduced for students and preceptors to assist with building community partnerships for implementing health promotion programs such as vascular risk reduction.
Conclusions: Students reported a reduction in feelings of isolation and valued opportunities to discuss patient care issues with peers as well as their preceptor. Faculty facilitated discussion of patient care experiences, and explored clinical reasoning, perceived boundaries of patient care roles and accountability for patient care outcomes. A student commented "this week I noticed that we have all gotten better at asking our peers about their thought process and why they made a specific decision or how they came to a conclusion. I think our ability to question our peers and ourselves helps us develop critical thinking skills and problem-solving abilities." More experience is required to explore optimal ways to integrate technologies for enhancing preceptor support and move the virtual classroom forward.

51. Preparing Pharmacy Students for Multicultural Practice in Canada – The Integration of Cultural Competence Into an Undergraduate Pediatrics/Geriatrics Module

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Objectives: To describe the development, delivery, and assessment of a cultural competence seminar integrated into a second year undergraduate pharmacy module.
Methods: Cultural competency was integrated into the undergraduate Pediatrics and Geriatrics module as a seminar. The seminar was delivered in collaboration with faculty members from Religious Studies, and Family Medicine. Student learning was assessed using written assignments, and short answer and multiple choice exam questions. Student evaluation of the seminar was assessed from course evaluations. Changes in delivery and content were implemented each year as a result of student comments and professor evaluation.
Results: The seminar has been delivered each year since the initiation of this course five years ago. The content included a short introductory lecture, followed by group work with students discussing multiple cases that focused on cultural issues related to health and health care delivery. Student marks on the cultural competence assignments and exam questions were consistent with scores on other assignments and exam questions. A self-assessment was introduced two years ago that resulted in a greater student acceptance of the overall topic. However, there remained a bimodal distribution of student feedback. Many students enjoyed the seminar and discussion, while others indicated that it was not beneficial to their learning needs. Feedback was overall supportive of the faculty involvement from Religious Studies.
Conclusion: The delivery of cultural competence was best facilitated in collaboration with faculty from Religious Studies. Students were overall engaged with the seminar material, and performed well on assignments and exams. A minority of students was unable to make the connection between the content and discussions, and pharmacy practice. This one seminar for second year students was successful, but further development of cultural competence training may be necessary to prepare pharmacy graduates to practice in Canada's multicultural environment.

52. Appetizers and Entrees: Who is Serving up What in the Classroom?

Colleen M. Brady HBSc(Bio), BSc(Pharm). University of British Columbia

Purpose: The new UBC BSc(Pharm) program, implemented in 2003, continues to evolve towards learning centered education. One of the strategies of importance in this move is students teaching students. This active learning strategy was implemented in September in a first year pharmacy course (PHAR 201: Pharmacist, Patient and Society). In the past, this first year course used traditional didactic lecture format to introduce the students to the Canadian health care system and current trends and challenges in pharmacy practice. Although this course was well received, students regularly commented that the subject matter was really dry and uninteresting and that they would prefer a delivery method that was more interactive and engaging. The purpose of this project was to redesign this course to enhance student engagement.
Methods: What did I do? Both instructor and student roles were revised. Through brainstorming

sessions amongst instructors the course was redesigned. Both instructors and students shared the teaching duties. Instructors provided content and at times, just an "appetizer" view of the material. Students "beefed" up some areas in the content. Each working group of students was given a set of objectives to address or a question(s) to answer or a newspaper article that related back to course material. Students were informed of their topic in the first class in September and presentations began in early October. A typical class included 60 minutes of instructor-taught material followed by 30 minutes of student-taught presentations. There were 25 groups consisting of six students.

Results: Students Perceptions of the change: Students found the presentations entertaining, good practice for public speaking and a great supplement to the lectures. Some commented on the social connections that were made while working in groups comprised of new classmates. Some enjoyed the creativity it allowed.

Conclusions: The instructors were elated over the quality of the presentations. Although it was time-consuming for the instructors in terms of coordination, with the students being more engaged and responsive in the class, this is something worth continuing.

53. Community Service Learning: Do Wellness Presentations to Seniors Improve Communication Competencies?

Colleen M. Brady HBSc(Bio), BSc(Pharm). Faculty of Pharmaceutical Sciences, University of British Columbia

Purpose: Service to the public and communication skills are competencies outlined in the framework of practice for pharmacists in British Columbia. The Faculty of Pharmaceutical Sciences at UBC has an ability-based outcomes curriculum. One of the ability-based outcomes for PHAR 303, a second year pharmacy skills course, is to communicate and educate effectively. In PHAR 303 students are required to create and deliver a presentation to a seniors group in the lower mainland on a given health topic. Marks for the presentation were based solely on the evaluation done by the pharmacist who attended the presentation. The pharmacist was either the instructor-in-charge of the course or was an appointed community pharmacist. Although, historically, students have performed well and have had positive comments about the course assignment, data has not been gathered on the impact of the presentations on the audience. The purpose of this project is to determine if the creation and delivery of a wellness presentation to seniors has helped students to improve their communication competencies.

Results: What have I done? To date, students have performed extremely well. Students have commented on course evaluations that they have enjoyed the experience of interacting with seniors and that it was a valuable exercise. Several thank-you cards and appreciative emails have been received from the various senior groups over the past few years acknowledging the students' efforts.

Conclusion: This is a great experience for students. Wellness presentations require students to disseminate newly acquired information to diverse audiences. It can be a huge leap for students to jump from learner to "teacher" or novice to "expert". Students have performed extremely well and have enjoyed the community involvement despite the initial anxiety. Seeking audience feedback could enhance the learning opportunity and exploring new methods for assessing student-learning needs to be done.

54. Facilitated Patient Interview as a Strategy to Improve Student Performance in an OSCE-based Pharmacy Practice Course

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Objectives: Primary objective was to determine for a 10 week OSCE-based pharmacy practice course if there is a statistically significant difference in the pass rate in the student-lead simulated patient interview (SLSPI) following an Enhanced Preparatory Practice Intervention (EPPI) when compared to the usual interventions (UI) used to prepare students. Secondary objective was to determine if a difference exists, does it persist in subsequent SLSPI interviews.

Methods: Students in all three years (2007, 2008, 2009) received the UI prior to evaluation of their first SLSPI. The UI included individual role-play with a simulated patient, receiving immediate verbal and written feedback on performance, in addition to an overall mark for their performance. Prior to the evaluation of the second SLSPI, the students in 2009 also received an EPPI. The EPPI included a demonstration of a patient interview performed by

the course instructor and facilitated by a specialist in patient communication and medication education. All students then participated in the usual SLSPI evaluation. The overall class pass/fail rate between the first and second SLSPI was compared among the three years. In addition the overall pass rate between the first, second and third SLSPI was compared within each year.
Results: The second interview pass rate for the 2007 and 2008, when UI was used, was not significantly different. The pass rate was significantly higher for 2009 when the EPPI was implemented, compared to the two preceding years (29.9%, 30.3%, 69.0% respectively, χ^2 = 89.297, P<0.001). The pass rate after the third patient interview showed no significant difference across all three years (67.0%, 59.3%, 66.8, respectively, χ^2 = 3.32, P= 0.190).
Conclusions: There was a statistically significant improvement in the pass rate in students who received the EPPI compared to UI. To allow the class to continue to improve at an accelerated rate a second strategically designed intervention should be considered.

55. The Use of a Direct Observation Booklet to Evaluate Students During a Community Pharmacy Rotation

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Objectives: In 2008, we started to use new evaluation tools in the clinical rotations of the Pharm.D. program including a direct observation booklet (DOB). The goals of the DOB were to allow the clinician to evaluate the student during a specific activity and to increase the chances of feedback to the student. It was recommended to clinicians to use the DOB at least once a day during a 4 week-rotation and to use it for different activities. The **objective** of this study was to evaluate the use of the DOB. More specifically, we were interested by the frequency of use, the activities that were evaluated with this tool and the respect of the guidelines.
Methods: All the DOB used during the first year-community rotation in 2008 were eligible to be reviewed. A random sample was chosen for this study. Each booklet was reviewed using a standardized collection sheet.
Results: Sixty booklets were reviewed for the periods of May and June of 2008. The DOB were used according to guidelines in most cases. It was used for an average of 17 times per student per 4-week rotation (min-max: 2-34). The DOB was mostly used to evaluate patient counselling and drug histories with an average of 20 (min-max: 2-32) and 5 (min-max: 0-31) times per DOB per student, respectively.
Conclusions: The direct observation booklet was used regularly and according to guidelines and for a variety of activities.

Pharmacy Practice Research

56. Nova Scotian Pharmacists' Knowledge and Experiences Providing the Emergency Contraceptive Pill

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Objective: In 2005 emergency contraception became more accessible to women when levonorgestrel (Plan B®) became available without a prescription in pharmacies. The objective of this research was to gather information about Nova Scotian pharmacists' knowledge of and professional experiences providing Plan B® to women since this regulatory change.
Methods: The research was conducted by anonymously surveying all pharmacists licensed to practice in Nova Scotia using a 25 item paper questionnaire sent via mail. The research was approved by the Dalhousie University Health Sciences Ethics Board.
Results: The response rate was 53% (594/1123). Of the 448 pharmacists who work in community pharmacy, 420 (93.8%) have provided Plan B® since the regulatory change. The most frequently reported average time to provide assessment and counselling was 6-10 minutes (48.0%), followed by <5 minutes (34.1%). Pharmacists are generally well informed about the therapeutics of Plan B® (90.2%-96.9%) However, pharmacists were less sure how often vomiting is caused by Plan B® (69.2% knew it is

less than 50% of the time) and just 39.1% knew that Plan B® can be effective if given up to 5 days after unprotected intercourse. Pharmacists requested additional training in the following areas: 1) improving communication and assessment skills (40.5%); 2) dealing with difficult situations, particularly cases of suspected assault (69.1%); and 3) where to obtain Plan B® free of charge (61.4%) and where to direct patients for sexually transmitted disease (STI) assessment (59.2%).
Conclusions: Undergraduate training of pharmacists and Continuing Pharmacy Education programs should focus on therapeutics (e.g. effectiveness window for Plan B® and rates of vomiting) and on improving communication and assessment skills, particularly in dealing with difficult situations that may arise when providing Plan B® . Information about alternate Plan B® providers and STI assessment locations should also be disseminated.

57. Validation of a Tool for Pharmacists and Health Professionals to Assess Intake, Knowledge, Attitudes, and Beliefs Regarding Calcium and Vitamin D

Cheryl A. Sadowski, Nese Yuksel. Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, Alberta, Canada.

Objective: To validate a questionnaire constructed to assess intake, knowledge, attitudes and beliefs of calcium and vitamin D in a young adult population.
Methods: This was a cross-sectional survey design. A 56-item self-administered questionnaire was developed with 6 sections (basic demographics, intake, knowledge, attitudes and beliefs of calcium and vitamin D), and a set of debriefing questions. Participants consisted of males and females at the University of Alberta (fall 2009), ages 18-35, willing to complete the questionnaire. Summary statistics were used for analysis.
Results: One hundred and three participants completed the questionnaire. Mean age was 21 years, 51% were female, and 59% were Caucasian. Most respondents were undergraduate students (58%), while 21% had completed a degree. Only 3 individuals found the questions difficult to understand and 10 found any questions unclear. However, 28 (27%) of participants found questions difficult to answer. Two participants noted that the questionnaire was too long, and one individual commented on wording. Thirteen percent of individuals had comments about the content, and this was broken down into 2 themes. The first was regarding food intake and the challenge of recording a typical day's intake. The second theme related to difficulty in questions related to vitamin D, as most respondents indicated poor knowledge about vitamin D sources, use, and role.
Conclusions: To promote intake, it is important to understand knowledge, attitudes and beliefs of calcium and vitamin D. This questionnaire may be a useful tool for pharmacists to provide targeted interventions for bone health, particularly in a young adult population who seem particularly unaware of vitamin D. The questionnaire was extremely well received by a well educated young adult population, with few revisions required for further testing and validation.

58. Community Pharmacists' Direct Access to Laboratory Values: An Exploratory Case Study

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Objectives: The implementation of Alberta Netcare provides community pharmacists access to vital patient health information, including laboratory values. The objectives of this study are to describe pharmacists' utilization of lab values provided in Netcare, examine the role of Netcare in community pharmacy practice, and explore factors related to the use of Netcare.
Methods: This qualitative study involved semi-structured, face to face interviews. A purposeful sample of six different community pharmacies participated in the study, and a total of 11 staff members from these pharmacies were interviewed. The interviews were recorded and subsequently transcribed verbatim. The transcripts were analyzed using qualitative data analysis software, NVivo, to identify codes and form themes.
Results: Netcare was primarily accessed to obtain patient demographic and medication information as opposed to lab values. For those pharmacists using Netcare lab values, pharmacists were mainly using lab values to monitor parameters of specific medications such as warfarin, hypoglycemics, and lipid lowering drugs. Factors influencing pharmacists' use of Netcare could be described using seven factors previously used to study practice change: practice experience and skills, remuneration for cognitive services, patient expectations,

pharmacy infrastructure, resources (such as staffing and time), professional relationships (with physicians), and external support (Netcare training, professional development courses on lab values). These factors can be both barriers and facilitators to lab value use, depending on the situation and setting.
Conclusions: Community pharmacists are caught between a dispensing practice and providing direct patient care as part of the health care team. Access to lab values through Netcare is just one of the many facilitators that will enable pharmacists to move towards a direct patient care practice. In this study, various factors were identified that contribute to use of Netcare lab values. We plan to use our knowledge of these factors to further study Netcare utilization and implementation on a broader scale, as well as better prepare pharmacy students to incorporate information from electronic records into direct patient care activities.

59. Searching for Even a Trickle of Flow and Engagement in the Practice of Pharmacy

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Objective: To determine if pharmacists experience engagement in practice and if so, identify intrinsic and extrinsic factors necessary for achieving the state.
Methods: Literature was searched using the terms happiness, engagement and well-being. From the results, Csikszentmihalyi's construct of flow as an experience necessary for engagement was selected to guide development of a 13 item pilot interview protocol examining:
A. Flow Components: Goals; Feedback; Matching skill to challenge
B. Resulting flow phenomena: Mental focus; Distraction exclusion; No worry of failure; No self-consciousness; Time distortion; Strength
C. Flow prerequisites: Expectations fulfilled; Autotelic experience; Control; Concerned Management.
Participants unknown to the researcher were recruited by referral from colleagues. Referring colleagues were instructed to refer pharmacists who they felt were engaged in their work. Referred participants were provided with study information including objectives, time commitment and data treatment and if agreeable, scheduled for an interview. Interviews were recorded, transcribed and analysed qualitatively for recurrent themes and interesting findings.
Results: Subjects included six identified participants all who agreed to be interviewed. They were female hospital pharmacists, four of whom were completing or recently completed a post-graduate Doctor of Pharmacy degree. Age ranged from early 20's to 40's and experience from 1 to 13 years. Data indicated the three flow components were irregularly present simultaneously and that participants did not achieve associated phenomena. Presence of all flow prerequisites were not identified by any participant. Pharmacists indicated during direct patient care activities alignment of the three flow components sometimes occurred but that associated flow phenomena were not attained.
Conclusion: Flow components inconsistently converged in the daily work of these pharmacists. Therefore, practitioners did not enjoy phenomena of complete focus to exclude distraction, elimination of worry and self-consciousness, time distortion and strength perception. Even if the components manifested concomitantly, absence of prerequisites may have precluded achieving flow. The sampled pharmacists did not experience engagement in their work.

60. Characterisation of Antibiotic Use in a Long-term Care Setting in the Edmonton Region: Do Bugs Need Drugs? A Multidisciplinary Team Approach

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Purpose: Antibiotic (abx) therapy in long-term care facilities (LTCFs) is widespread and frequently inappropriate resulting in inadequate therapy and increased risk of abx resistance. Antibiotic therapy in respiratory tract infections (RTIs) and urinary tract infections (UTIs) was evaluated in two LTCFs in Edmonton, Alberta.
Methods: Appropriateness of abx therapy of UTIs and RTIs was evaluated by retrospective chart review based on regional guidelines for antimicrobial use (Bugs and Drugs 2006), results of culture and sensitivity, and local antibiograms.
Results: Ninety-two prescriptions were evaluated within two LTCFs. Antibiotics most frequently prescribed were ciprofloxacin (31.5%),

cotrimoxazole and nitrofurantoin (each 16.3%). Of 67 prescriptions for UTI, 77.6% were inappropriate. Of 16 prescriptions for RTI, 100% were inappropriate. In 9 patients (9.8%), for whom the indication for abx treatment was unclear, 100% were inappropriate. Documented resistance to the chosen antimicrobial agent was one of the most common reasons that antibiotic use was inappropriate. Nitrofurantoin was frequently inappropriate due to risks of using nitrofurantoin in patients with renal insufficiency such as the elderly.

Conclusions: Overall, 77.6% of antibiotics for UTI, 66.8% for RTI, and 100% for "unclear" indications were inappropriate. Cotrimoxazole, ciprofloxacin and nitrofurantoin were the most commonly prescribed agents in these LTCFs. Cotrimoxazole and ciprofloxacin are commonly used first line agents in the treatment of UTIs, and are listed as such in Bugs and Drugs 2006. However, resistance of *E. coli* to cotrimoxazole and ciprofloxacin has increased to 38% and 55% respectively in LTCFs in Edmonton (2006 antibiogram), precluding their use as first line empiric therapies for UTIs. In addition, nitrofurantoin, is not appropriate in the elderly population with CrCl <60ml/min, a frequent occurrence. Important issues exist with UTI and RTI treatment in this population and additional work is required to elucidate more effective management strategies.

Social and Administrative Research

61. Canadian Drug Evaluation Capacity: a Looming Crisis

Judith A. Soon[1], Matthew O. Wiens[2], Stuart M. MacLeod[3], Sunaina Sharma[4]. [1] UBC Faculty of Pharmaceutical Sciences [2]UBC School of Population & Public Health [3]Child and Family Research Institute [4]Community of Federal Regulators, Health Canada.

Objectives: Health Canada has undertaken to modernize the regulation of pharmaceuticals and biologics to facilitate the ongoing monitoring of safety and effectiveness throughout the life cycle of drug products. Prior to implementation, Health Canada requested the authors to identify and describe the programs in Canadian post-secondary educational institutions able to train graduate students in post-market drug evaluation research (PMDER) methodology. Study findings will inform future training opportunities for research scientists in this area.

Methods: The conduct of the institutional inventory was web-based, with telephone follow-up. All health-related graduate programs offering courses in epidemiology and biostatistics were eligible, as well as graduate programs in pharmacy, epidemiology, public health and health informatics. The prevalence of relevant courses was summarized by institution and the estimated number of graduate students calculated.

Results: Twenty-one **(**21) Canadian institutions were eligible for inclusion in the inventory including the ten institutions with Faculties and Schools of Pharmacy. Across the country, 31 MSc and PhD thesis-based degree programs are available, graduating about 500 MSc and PhD students annually, although most are not specific to PMDER. The six core courses deemed essential for training in PMDER was determined for each institution: Epidemiology (21); Biostatistics (19); Health Economics/ Pharmacoeconomics (15); Pharmacoepidemiology (4); Pharmacogenetics/Pharmacogenomics (4); and Patient Safety/Risk Management/Pharmacovigilance (4). While no institution offered all six courses, four (McGill University, Université Laval, Université de Montréal and University of Ottawa) offered five core courses.

Conclusions: Given the lack of standardization of curriculum, the number of graduating MSc and PhD research scientists is insufficient to meet future needs in post market drug evaluation. Recommendations include support for a national syllabus that would guide universities interested in training highly qualified personnel, encouragement of the development of a national scholarship program for graduate students in this specialized research field, and CIHR Canada Research Chairs in Therapeutic Risk Management in selected Canadian post-secondary institutions.

62. Corporate Social Responsibility in the Canadian Pharmaceutical Industry

Tim West and *Roy Dobson*. College of Pharmacy & Nutrition, University of Saskatchewan, Saskatoon, Saskatchewan.

Background: Corporate social responsibility (CSR) is the engagement by business in activities or programs beyond the maximizing of shareholder value; to engage in a variety of activities that are in the interests of a wide range of stakeholders, both within and outside the company. The pharmaceutical industry is noted for participating in CSR on a voluntary basis. A review of the literature leads to the conclusion that the use of CSR is expanding in its importance and application within the pharmaceutical industry.
Objective: Using a constructionist grounded theory methodology, examine CSR within the Canadian and American pharmaceutical industries; specifically, as it pertains to the gap in the literature regarding the relationship between motivations and values in CSR decision-making.
Results: Analysis of 7 interviews with employees of 4 pharmaceutical companies that are operating in Canada has been completed. Emerging main categories include: 1) Required top-down adoption for authenticity; 2) Evolution of CSR through focus and differentiation; 3) Complex and varying mix of motivations and drivers; and 4) CSR as a mind-set which provides new skill sets.
The Next Step: Conduct additional interviews and collect secondary data in Canada and the US until theoretical saturation has been reached. The result will be a multi-narrative, substantive theory for CSR within the Canada and American pharmaceutical industries.

University Posters

63. University of Alberta

64. University of Manitoba

65. University of Toronto

66. University of Montreal

67. Dalhousie University

CSPS
Poster Presentations
Day 2
Friday, June 4, 2010

Day 2

Biomedical Sciences

68. Development of Short-hairpin RNA that Targets Intracellular Signalling Molecule – Smad1

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Purpose: Smad1 is an intracellular signalling molecule and mediates signal transduction of transforming growth factor beta and bone morphogenetic protein receptors. Once Smad1 is activated it forms a complex with Smad4, which moves into the nuclei and binds to specific DNA sequence to regulate gene expression. It has been documented that the increased expression and phosphorylation of Smad1 may play an important role in organ fibrogenesis such as liver fibrosis and systemic sclerosis. Therefore, inhibition of Smad1 expression would attenuate the development and/or progression of organ fibrosis. The current study was to develop a short-hairpin RNA (shRNA) that targets Smad1 in hepatic stellate cells.
Methods: shRNA for rat Smad1 was designed according to the rat Smad1 sequence from Genbank by BLOCK-iT™ RNAi Designer**,** a tool at the Invitrogen company's website. BLOCK-iT Adenoviral RNAi Expression System was employed to deliver shRNA into hepatic stellate cells. pLP-Adeno-X-CMV was employed to deliver Smad1 into hepatic stellate cells. The immortalized rat hepatic stellate cell line (CFSC-8B) was cultured in DMEM with 10% FBS. Total RNA and protein were extracted for RT-PCR and Western blot analyses.
Results: shRNA for Smad1 and Smad1 cDNA was successfully constructed into adenovirus. Infection of adenovirus withSmad1 siRNA significantly inhibited the expression of Smad1 in CFSC-8B cells at both RNA and protein levels. Moreover, Smad1 siRNA transformed CFSC-8B cells into a phenotype that was similar to quiescent hepatic stellate cells. Infection of adenovirus with Smad1 significantly increased the abundance of Smad1 RNA and protein.
Conclusion: Smad1 and shRNA of Smad1 were successfully delivered into hepatic stellate cells and a short-hairpin RNA of Smad1 had been demonstrated to inhibit the expression of Smad1 in hepatic stellate cells.

69. Modulation of Cardiac Metabolism by β-blockers During Diabetes: A Role in Apoptosis Signaling

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Purpose: One cardiovascular complication associated with diabetes mellitus (DM) is a cardiomyopathy that can occur in the absence of valvular or ischemic heart disease and in normotensive patients with excellent glycemic control. Diabetic cardiomyopathy can progress to heart failure if not managed. The cardiomyopathy observed may be due to a loss of contractile tissue as a result of apoptosis. Apoptosis may be caused by oxidative stress associated with metabolic and signaling modifications that precedes the development of dysfunction. Chronic treatment with beta-adrenergic receptor antagonists (β-blockers) improve function. Metoprolol and carvedilol are clinically important β-blockers that have also been shown to favorably modulate metabolism; in addition, carvedilol, has been shown to have biologically relevant antioxidant properties. Preliminary *in vivo* data indicates that metoprolol can reduce apoptosis in the diabetic heart and ameliorate diastolic dysfunction. Currently, there is no specific treatment for diabetic cardiomyopathy. β-blockers may serve as a novel treatment option.
Methods: We employed a streptozotocin (STZ) induced rat model of type 1 DM. Animals received a one-time dose of 60 mg/kg body weight and the presence of DM was confirmed by measurement of blood glucose levels 3 days post injection. Two weeks post STZ, osmotic pumps containing β-blockers were installed. Metoprolol and carvedilol were delivered at a rate of 15 and 10 mg/kg/day, respectively. In order to assess the significance of

carvedilol's antioxidant abilities, some metoprolol treatments were supplemented with vitamin C, delivered at 1000 mg/kg/day. A six and eight week time point were studied to assess changes before and after development of cardiomyopathy.
Results: Analysis of plasma indicates successful induction of DM, with an approximate 2.5-fold increase in blood glucose levels in STZ treated rats. Diabetic animals showed significant reduction in rates of glucose oxidation, however, animals that were diabetic for six weeks showed no cardiomyopathy as assessed by echocardiography and working heart perfusion.
Conclusion: Analysis of effects of β-blockers, as well as assessment of protein expression, apoptosis and oxidative stress remains. The eight week time point is in progress.

70. Effect of Phenobarbital on Markers of Cell Viability, Oxidative Stress, and Necrosis in Primary Cultures of Rat Hepatocytes Treated with Valproic Acid

Jayakumar Surendradoss, Frank S. Abbott, and Thomas K. H. Chang. Faculty of Pharmaceutical Sciences, The University of British Columbia, Vancouver, BC, Canada.

Purpose: Valproic acid (VPA) is associated with a rare but fatal idiosyncratic hepatotoxicity. Proposed mechanisms for this hepatotoxicity include formation of reactive metabolites of VPA, inhibition of mitochondrial β-oxidation of fatty acids, and development of oxidative stress. VPA undergoes extensive hepatic biotransformation, and the extent is increased by phenobarbital and other inducers of various drug-metabolizing enzymes (e.g. CYP2B). Retrospective studies of fatal cases in patients who were taking VPA suggest that concurrent therapy with phenobarbital is a potential risk factor in the development of the hepatotoxicity, although subsequent controlled *in vivo* studies in rodents have produced conflicting results. In the present study, we employed a cell culture model to investigate directly the effect of phenobarbital on the cytotoxicity of VPA.
Methods: Hepatocytes were isolated from adult male Sprague-Dawley rats and plated in a sandwich configuration with Matrigel™. Cultured hepatocytes were pretreated with sodium phenobarbital (100 μM) or culture medium (vehicle control) for 72 h, and subsequently treated with varying concentrations (0.3-100 mM) of VPA (the sodium salt) or culture medium (vehicle control) for 24 h. Conversion of 4-[3-(-4-iodophenyl)-2-(4-nitrophenyl)-2*H*-5-tetrazolio]-1,3-benzene disulfonate (WST-1) to formazan (a marker of cell viability), oxidation of 2',7'-dichlorofluorescin to 2',7'-dichlorofluorescein (DCF; a marker of oxidative stress), and cellular release of lactate dehydrogenase (LDH; a marker of necrosis) were measured. CYP2B-mediated enzyme activity was measured by the 7-benzyloxyresorufin *O*-dealkylation (BROD) assay. Levels of VPA metabolites were quantified by gas chromatography-mass spectrometry.
Results: Initial experiments confirmed that treatment of cultured hepatocytes with phenobarbital increased BROD activity. Phenobarbital also increased the levels of 4-ene-VPA, 2,4-diene-VPA, 3-OH-VPA, 4-OH-VPA, 5-OH-VPA, 3-keto-VPA and 4-keto-VPA, whereas it had little or no effect on the levels of 2,3'-diene-VPA, 2-ene-VPA, or 3-ene-VPA. VPA treatment decreased the formation of formazan, elevated the levels of DCF, and increased the cellular release of LDH. However, the magnitude of these cytotoxic effects of VPA was not altered by pretreatment of hepatocytes with phenobarbital.
Conclusion: Modulating the enzymatic formation of VPA metabolites by phenobarbital is not accompanied by changes in the magnitude of VPA cytotoxicity in primary cultures of rat hepatocytes.
Acknowledgements: This research was supported by the Canadian Institutes of Health Research (Grant MOP-13744) and Michael Smith Foundation of Health Research (senior scholar award to T.K.H.C.).

71. Prodrug Development to Stimulate Bone Growth and Simultaneously Inhibit Bone Decay

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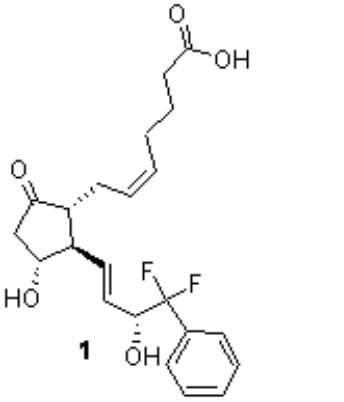
Purpose: This proposed project seeks to address a critical medical need in Canadians and world populations for the treatment of osteoporosis.
Methods and Results: Prostaglandin E2 (PGE2) (**1**) has been shown to stimulate bone growth in rats and humans via activation of the EP4 subtype receptor but it has unacceptable gasterointestinal (GI) side effects.[1] EP4 receptor selective agonists such as the tetrazole **2** also stimulate bone growth but are still associated with some of the GI side effects.[2] Antiresorptive bisphosphonate drugs (BPs) such as

alendronate **3** are known to target and irreversibly bind to bone and conjugates of PBs and drugs have been used in the past to target drugs to bone.[3] We have developed novel prodrug conjugates where **2** and **3** are joined through an enzymatically or chemically hydrolyzable linker such that after dosing the conjugate is taken up into bone and then subsequently liberates the two active substances *in situ* over time.



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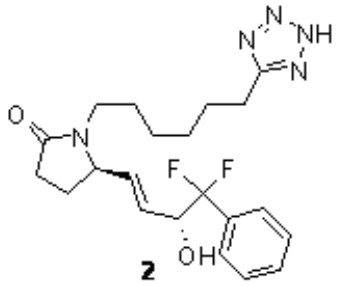

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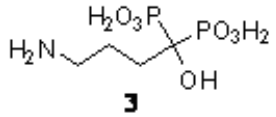

3

Conclusion: The conjugates were synthesized with radiolabelled components to allow us to monitor uptake and release *in vivo* in rats. The presentation will cover the exciting recent success of the project focusing the synthesis and bone uptake.

References:

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72. Naturally Occurring Variants of Human Aldo-keto Reductases Alter *in vitro* *M*etabolism of Doxorubicin and Daunorubicin

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Purpose: Doxorubicin (DOX) and daunorubicin (DAUN) are highly effective anthracycline anti-cancer drugs; however, considerable interpatient variability exists in their pharmacokinetics. This variability is likely due to altered metabolism by non-synonymous single nucleotide polymorphisms (ns-SNPs) in genes encoding a class of NADPH-dependent oxidorectuases, the aldo-keto reductases (AKRs). This study examines the effect of naturally occurring ns-SNPs in seven *AKR* genes, AKR1B1, AKR1B10, AKR1C1, AKR1C2, AKR1C3, AKR1C4, and AKR7A2, on the *in vitro* metabolism of anthracyclines doxorubicin and daunorubicin to their major metabolites, doxorubicinol and daunorubicinol.

Methods: Kinetic assays measured metabolite levels by HPLC separation with fluorescence detection using purified, histidine-tagged, human AKR wild-type and variant enzymes and the following Michaelis-Menten parameters were compared: maximal rate of activity (V_{max}), substrate affinity (K_m), turnover rate (k_{cat}), and catalytic efficiency (k_{cat}/K_m).

Results: Only certain variants for AKR1C3, AKR1C4 and AKR7A2 exhibited significant difference in these parameters compared to the wild-type. In the presence of DAUN, the A106T, R170C, and P180S variants significantly reduced metabolism compared to the AKR1C3 wild-type (V_{max}: 23-47% decrease; k_{cat}: 22-47% decrease, k_{cat}/K_m: 38-44% decrease), but did not alter the K_m. Only one variant for AKR1C4 (L311V) was found to have significantly reduced activity as demonstrated by a decrease in V_{max} (47% lower) as

well as k_{cat} and k_{cat}/K_m (both 43% lower). In addition, the A142T variant was found to significantly alter all kinetic parameters compared to the AKR7A2 wild-type (V_{max} and k_{cat}: 61% decrease; K_m: 156% increase; k_{cat}/K_m: 85% decrease). With DOX as a substrate, the R170C and P180S variants reduced V_{max} and k_{cat} for DAUN metabolism significantly (V_{max}: 41-44% decrease; k_{cat}: 39-45% decrease) compared to the AKR1C3 wild-type. K_m was only significantly altered for the P180S variant (92% increase) while the k_{cat}/K_m values for both variants were significantly lower than the wild-type (52-69% decrease). Also, the A142T variant was found to significantly alter all kinetic parameters compared to the AKR7A2 wild-type (V_{max}: 41% decrease; k_{cat}: 44% decrease; K_m: 47% increase; k_{cat}/K_m: 60% decrease). Furthermore, by comparing k_{cat}/K_m values, we observed that DAUN is a better substrate for the AKR wild-type and variant enzymes compared to DOX (2.4-8.2 fold higher for AKR1C3, 2.5-4.5 fold higher for AKR1C4, and 6.0-17.1 fold higher for AKR7A2).

Conclusion: These findings suggest that commonly occurring ns-SNPs in human AKR1C3, AKR1C4, and AKR7A2 significantly alter the *in vitro* metabolism of DOX and DAUN.

73. Cellular Antioxidant Effect of Diltiazem and Silymarin

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Purpose: Silymarin and low dose d-diltiazem are known to possess hepatoprotective properties. Diltiazem is a hydrophilic drug while silymarin is lipophilic. This suggests that these drugs have protective effects on different parts of the liver cell. We hypothesized that the use of low dose diltiazem with silymarin would yield an additive effect as a hepatoprotectant during periods of oxidative stress.

Methods: To measure the relative protective effect of these drugs on the liver, an oxidative stress model was used. PLC hepatocytes were treated with d-diltiazem and/or silymarin for 24 hrs at 37°C followed by incubation with H_2O_2 to initiate oxidative stress. Additional comparisons were made with Vitamin E and Trolox (used as controls) to observe the relative antioxidant capacities from our treatment regime. The dichlorofluorescein (DCF) assay was used to assess the extent of reactive oxidative species (ROS) in the liver cells. The effect of d-diltiazem, silymarin, Trolox, and Vitamin E on the cellular proliferation was determined using the WST-1 assay.

Results: DCF assays showed that diltiazem, and silymarin significantly decreased ROS levels. Combinations of low-dose diltiazem and silymarin contributed to further reductions in ROS. Measuring cell proliferation via the WST-1 assay also showed significant increases in cell viability with drug treatment.

Conclusion: Use of diltiazem or the combination diltiazem and silymarin showed some marked improvements in cell viability. Use of diltiazem and or diltiazem and silymarin has merit in use as a hepatoprotectant.

74. Inhibition of Soluble Epoxide Hydrolase Confers Cardioprotection Against Benzo(a)pyrene–induce Cardiac Hypertrophy in Rats

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Purpose: We recently demonstrated that benzo(a)pyrene (BaP , one of the constituents of cigarette smoke) causes cardiac hypertrophy by altering arachidonic acid metabolism through the induction of the expression of CYP ω-hydroxylases enzymes such as CYP1A1, 1B1, 2E1, 4F4, 4F5, and soluble epoxide hydrolase (sEH). CYP ω-hydroxylases are known to metabolize arachidonic acid to the cardiotoxic metabolite, 20-hydroxyeicosatetraenoic acid, whereas sEH metabolize the cardioprotective metabolites, epoxyeicosatrienoic acids to dihydroxyeicosatrienoic acids. Interestingly, we have previously demonstrated that inhibition of CYP ω-hydroxylase enzymes partially reversed BaP-induced cardiac hypertrophy. Therefore, it is important to examine whether the inhibition of sEH confer cardioprotection.

Methods: Male Sprague Dawley rats were injected intraperitoneally daily with either BaP (20 mg/kg) or the combination of BaP (20 mg/kg) and sEH inhibitor, TUPS (0.65 mg/kg) for 7 days. Thereafter, the heart, liver and kidney were harvested, and the heart to body weight ratio was determined. The

expression of the hypertrophic markers; atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) and *CYP* genes were determined by real-time polymerase chain reaction.

Results: Our results clearly demonstrate that treatment with BaP alone significantly induced the gene expression of CYP ω-hydroxylase enzymes, CYP1A1, 1B1, 2E1, 4F4, and 4F5 in the heart, liver and kidney. On the other hand, treatment with sEH inhibitor, TUPS significantly reversed the BaP-mediated induction of the hypertrophic markers, ANP and BNP. In addition, TUPS completely prevented the increase in the heart to body weight ratio induced by BaP. Co-treatment with BaP and TUPS significantly reversed the induction in the gene expression of CYP1A1, 1B1 and 4F4 only in the heart but not in the liver or the kidney.

Conclusion: The current study demonstrates the cardioprotective effect of sEH inhibitor against BaP-induced cardiac hypertrophy and further confirms the role of sEH in the development of cardiac hypertrophy.

Acknowledgement: This work was supported by a grant from the Heart and Stroke Foundation of Alberta, NWT, and Nunavut to AOSE. MEA and BNMZ are the recipients of Egyptian Government Scholarships.

75. Harman is a Novel Aryl Hydrocarbon Receptor Ligand

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Purpose: Harman is a common compound in coffee brews, tobacco smoke and overcooked foods. Several studies have demonstrated its mutagenic and carcinogenic effects; however, the exact mechanism is not fully identified. In the present study, we examined the ability of harman to induce the carcinogen-activating enzyme, cytochrome P450 1A1 (CYP1A1) in human hepatoma HepG2 cells.

Methods: The cytotoxicity of harman was assessed using the MTT assay. The effects of different concentrations of harman (1-50 μM) on CYP1A1 mRNA and protein levels were determined using real-time polymerase chain reaction and Western blot analysis, respectively. CYP1A1 catalytic activity was determined using 7-ethoxyresorufin as a substrate. The role of aryl hydrocarbon receptor (AhR)-dependent mechanism was determined using HepG2 cells transiently transfected with the XRE-driven luciferase reporter gene and electrophoretic mobility shift assay.

Results: Our results showed that harman had no apparent cellular toxicity effects up to 50 μM. In addition, harman significantly induced CYP1A1 mRNA in a time- and concentration-dependent manner with a maximum induction at 6 h and 50 μM, respectively. The RNA polymerase inhibitor, actinomycin D, completely blocked the CYP1A1 mRNA induction by harman, indicating a requirement of *de novo* RNA synthesis through transcriptional activation. Similarly, harman significantly induced CYP1A1 at protein and activity levels in a concentration-dependent manner. Moreover, the AhR antagonist, resveratrol, inhibited the increase in CYP1A1 activity by harman. The ability of harman to induce CYP1A1 was strongly correlated with its ability to stimulate AhR-dependent luciferase activity and electrophoretic mobility shift assay, suggesting that AhR-dependent mechanism is involved.

Conclusion: This is the first demonstration that harman can directly induce CYP1A1 gene expression in an AhR-dependent manner and may represent a novel mechanism by which harman promotes mutagenicity and carcinogenicity.

Acknowledgements: This work was supported by NSERC to A.E. M.E. is the recipient of Egyptian Government Scholarship.

76. The Effect of Nrf2 Knockout on the Constitutive Expression of Drug Metabolizing Enzymes in C57Bl/6 Mice Livers

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Purpose: Cellular defense mechanisms to counteract the cancer induction are partially controlled by the transcription factor nuclear factor erythroid-2 related factor-2 (Nrf2) which controls the phase II drug metabolizing enzymes (DMEs) directly, and phase I DMEs indirectly through affecting their upstream regulators. Therefore, the aim of the current study is to examine the level of both phase I and phase II DMEs and their related

transcription factors in the Nrf2 knockout model.
Methods: The levels of phase I and phase II DMEs in the livers of Nrf2 knockout and wild type (C57Bl/6) mice were determined at mRNA, protein and catalytic activity levels. In addition, we measured the mRNA, and protein expression levels of the main transcription factors controlling phase I and phase II DMEs.
Results: Our results showed that phase I cytochrome P450s (CYPs), namely, Cyp1 family, Cyp2b10, and Cyp3a11, mRNA, protein, and catalytic activity levels were significantly decreased in the livers of Nrf2 knockout mice compared to wild type. Furthermore, phase II DMEs that are under the control of Nrf2 typified by NAD(P)H: quinone oxidoreductase 1 (Nqo1), and glutathione *S*-transferase (Gst) were decreased at the mRNA, protein, and catalytic activity levels in the livers of Nrf2 knockout mice compared to wild type. In addition, our results showed that aryl hydrocarbon receptor (AhR), constitutive androstane receptor (CAR), and pregnane X receptor (PXR) mRNA, and protein expression levels were decreased in the livers of Nrf2 knockout mice compared to wild type, suggesting that the decrease in DMEs in Nrf2 knockout mice is due to the decrease in transcription factors controlling them.
Conclusion: We conclude that knockdown of Nrf2 causes disruption to the coordination of phase I and phase II drug DMEs and thus confound results that are dependent on these enzymes. This work was supported by NSERC Discovery Grant RGPIN 250139-07 to A.O.S. A.A-M. is the recipient of Alberta Ingenuity Graduate Scholarship.

77. Differences in Once a Day Nifedipine Pharmacokinetic Profiles Lead to Clinically Relevant Changes

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Purpose: Adalat® XL® is a unique non-dispersable tablet formulation of a bilayer of nifedipine and osmotic polymer surrounded by a semi-permeable shell. The osmotic system delivers nifedipine at a zero order rate producing smooth, consistent nifedipine plasma levels, resulting in proven optimal blood pressure control. Mylan nifedipine extended release is a homogenous mixture of drug and osmotic agent in a monolayer delivery system and has a different dissolution profile. A recent pharmacokinetic (PK) study comparing the two formulations demonstrated distinct differences between the two osmotic release systems (Anschutz et al. Int J Clin Pharmacol Ther 2010: 48; 158). The monolayer formulation showed a prolonged initial release lag time and reduced plateau phase. Under the fed state, AUC(0-tlast) and Cmax were low enough to fall outside of the bioequivalence range. The clinical implications of these PK differences were investigated in hypertensive patients since the blood pressure (BP) response to nifedipine is known to be closely correlated with plasma drug concentration.
Methods: BP response to the different formulations was demonstrated in a case series of N=1 studies. Specifically, in 3 patients, the formulation was switched back and forth 4 or 5 times at weekly intervals with home BP monitoring. Spontaneously-reported adverse events associated with formulation switches in the general patient population were also analysed.
Results: BP monitoring showed lower systolic BP (SBP) values with the bilayer formulation ($p<0.001$), and consistent increases in SBP when switching from the bilayer to monolayer formulation. In all but one instance, increases were 9 mmHg or higher. Over 30 adverse events were reported after patients switched from bilayer to monolayer formulation. More than 30% were lack of blood pressure control or worsening of angina, and at least 6 events were considered serious in nature.
Conclusion: Differing the formulation of once a day extended-release nifedipine impacts the ability to effectively control blood pressure, and ultimately could lead to negative cardiovascular outcomes. The Canadian Hypertension Education Program Recommendations highlight that increases of as little as 2 mmHg SBP increase rates of mortality due to stroke and CHD. This clearly demonstrates the need to show therapeutic equivalence when delivery technologies are substituted.

78. Qualitative Investigation of Barriers to Accessing Health Services by Injection Drug Users in Saskatoon Health Region

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Purpose: BRIDGE Saskatoon (Building Relationships with Injection Drug users for Greater Engagement) is a health focused community-based partnership. It was developed in 2007 with the aim of creating synergy among individuals involved in injection drug services, research and policy. The partnership consists of four pillars: health promotion & primary prevention, harm reduction, enforcement, and treatment & recovery. The goal of the treatment & recovery group is to develop a communication strategy within the continuum of care of health services in Saskatoon so that individuals who inject drugs can receive the best services available during a time of crisis. The aim of this project is to assess crisis services offered in Saskatoon, using information collected from injection drug users (IDU).
Methods: Qualitative methodologies (focus groups and interviews) are used. Participants were recruited with the assistance of two community organizations, AIDS Saskatoon and Communities for Children. Two hour-long adult focus groups (one male group, and one female group) and sixteen personal interviews with youth were conducted. Data was recorded by note-taking or audio taping. Content analysis was performed, where similar concepts were combined into groups, and from these groups, major themes were determined.
Results: Alongside information originally collected by the Saskatoon Health Region, the focus groups reaffirmed the need to increase service provision. Six barriers to care were identified by participants: Lack of resources and inefficient policy, discrimination, unsupportive family or detrimental peer influence, inadequate communication & co-ordination with and between service providers, unsatisfactory provider education regarding substance abuse, and insufficient finances and resources. Conversely, there were many services that participants found helpful and effective. The findings indicate differences between the three demographic groups. The female group had more problems with housing, the youth group with family, and the male group expressed the most interest to be part of the solution.
Conclusion: Many barriers to service access were identified by injection drug users. However, in order to achieve a more complete understanding of access to services in Saskatoon, focus groups will be held with service providers in the near future.

79. Disease-Drug Interaction: Reduces Response to Verapamil Despite Increased Concentration in Active Crohn's Disease

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Purpose: Inflammation is involved in the pathogenesis of cardiovascular diseases and is associated with increased mortality in post-myocardial infarction. This may, in part, be explained by reduced response to pharmacotherapy. Rheumatoid arthritis (RA) results are reduced response to verapamil despite an elevated drug concentration. We investigated whether verapamil pharmacokinetics and pharmacodynamics are influenced by inflammation of the bowel disease (Crohn's disease).
Method: We administered 80 mg verapamil orally to Healthy controls (Healthy, n=9), Crohn's in remission (REMISSION, n=22) and active Crohn's (ACTIVE, n=14). Blood sample were taken for analysis of inflammatory mediators and verapamil enantiomers, also blood pressure and ECG were recorded.
Results: Verapamil prolonged PR interval in all patients (mean maximum 8-15% in 30 min). A significant negative correlation was found between the response and the disease activity measured as the Harvey-Bradshaw Index (HBI) ($r= 0.86$, $p<0.0001$). Due likely to the high inter-subject variability associated with disease severity, no significant differences were observed between three groups in terms of the mean ECG response and mean inflammatory mediators concentrations. However, despite the observed HBI-dependent reduced response in ACTIVE, significantly increased plasma S-verapamil concentration was noted as compared

with other groups (AUC, mg min/L: HEALTHY, 3.7 ±2.8; REMISSION, 5.7 ±8.4; ACTIVE, 32.1 ±35.9).
Conclusion: Active Crohn's causes reduced response to verapamil despite increased plasma concentration due, likely, to down-regulations of both hepatic enzymes and calcium channel target proteins. Controlling of the Crohn's disease tends to restore plasma protein levels and hepatic drug metabolism resulting in relatively normal verapamil pharmacokinetics and pharmacodynamic. Since patients in remission demonstrate normal response, effective control of the disease seems essential in preventing cardiovascular events in Crohn's patient.
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Drug Delivery and Pharmaceutical Technology

80. Peritoneal Retention and Tissue Distribution of Labeled Liposomes after Intraperitoneal Injection to Mice: Effects of Lipid Composition and PEG Coating

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Purpose: In the treatment of peritoneal carcinomatosis, systemic chemotherapy is not quite effective due to the poor penetration of cytotoxic agents into the peritoneal cavity; whereas intraperitoneal administration of chemotherapeutic agents, besides causing local irritation and toxicity, is generally accompanied with quick absorption of the free drug from the peritoneum. Local delivery of drugs as controlled-release delivery systems like liposomes could provide sustained and higher drug levels and reduce local and systemic toxicity. In order to achieve more appropriate liposomal formulations with higher peritoneal exposure, this study was aimed to investigate the effects of phospholipid composition and surface PEGylation on the peritoneal retention, blood levels and tissues distribution of liposomes.
Methods: Conventional liposomes composed of Distearoyl (DSPC), Dipalmitoyl (DPPC) or Dimiristoylphosphatidylcholine (DMPC) and cholesterol (CHOL) (molar ratio 2:1) or PEGylated liposomes composed of DSPC/CHOL/PEG_{2000}-DSPE (molar ratio 2:1:0.2) were prepared at two sizes of 100 and 1000 nm. Subsequently, these liposomes were labeled with ^{99m}Tc and injected into mouse peritoneum. Then mice were sacrificed at 8 different time points and the percentage of injected radiolabel in the peritoneal cavity and tissue distribution in terms of percent of the injected dose/gram tissue (%ID/g) were obtained.
Results: All conventional liposomes showed a much greater retention in the peritoneum compared to the free label. The ratio of peritoneal AUC to the free label ranged from 4.88-8.21 to 11.06-15.51 for 100 nm and 1000 nm liposomes respectively. Among all tested liposomal formulations the greatest peritoneal retention was obtained with DSPC/CHOL 1000 nm. For small lposomes, DSPC/CHOL/PEG vesicles had the greatest peritoneal level, although not significantly different from the other same sized vesicles. DSPC/CHOL/PEG 1000 nm vesicles were unstable and had almost the lesser retention among all particulate formulations, with an AUC only 5.09 fold that of control. DSPC/CHOL/PEG 100 nm due to its relatively greater peritoneal retention entered more slowly in the systemic circulation, the C_{max} was attained 4 hours after injection vs. 2 hours for other particulate formulas, but its level remained stable between 7 and 24 hours. DSPC/CHOL/PEG 1000 nm due to its instability showed the greatest concentration in the spleen with a huge difference from the other 1000 nm formulas.
Conclusion: In conclusion, among different tested samples the greater peritoneal retention was obtained with DSPC/CHOL 1000 nm vesicles.

81. Pulmonary Toxicity of Polysorbate-80-coated Inhalable NPs; *in vitro* and *in vivo* Evaluation

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Purpose: This study was designed to investigate the impact of polysorbate 80, as nanoparticles (NPs) coating material, on the pulmonary toxicity of inhalable NPs in vitro and in vivo.
Methods: The biophysical interaction of coated NPs with a lung-surfactant model was assessed in vitro. Changes in the Surface Pressure-Area Isotherm of a monolayer film of 1,2-Dipalmitoyl-sn-Glycero-3-Phosphocholine (DPPC) on top of a subphase of distilled water containing polysorbate 80, non-coated NPs or polysorbate-80-coated NPs were recorded and compared. The in vivo pulmonary toxicity of the previously mentioned NPs formulations was assessed using Balb/C nude mice.
Results: NPs affected the isotherm of the DPPC monolayer differently depending on the use of polysorbate 80 as coating material. The collapse pressure of the DPPC monolayer film was significantly decreased by the addition coated NPs when compared with DPPC alone, 27.3±2.2 and 53.4±3.7, respectively. Mice that received coated inhalable NPs suffered from breathing difficulties and respiratory distress. The histology study showed clear acute terminal micro hemorrhages from the alveolar capillaries accompanied by local flooding of many alveoli with protein rich fluid. Mice treated with non-coated NPs showed no pathological difference when compared with control mice.
Conclusion: Polysorbate-80, as NPs coating material, enhanced the biophysical interaction of NPs with the components of a DPPC monofilm resulting in disruption of the monolayer integrity *in vitro*. Destabilizing the surfactant monlyaer film was associated, *in vivo*, with acute pulmonary toxicity. Studying the changes in surface pressure-area isotherm, *in vitro,* may serve as an early assessment for the *in vivo* tolerability for different inhalable treatments.

82. Isothermal Microcalorimetry as a Quality by Design Tool to Determine Optimal Blending Sequences

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Purpose: This study was designed to assess the value of isothermal microcalorimetry (ITMC) as a Quality by Design (QbD) tool to choose suitable blending conditions during tablet preparation.
Methods: Powder mixtures that contain micro crystalline cellulose (MCC), dibasic calcium phosphate dihydrate (DCPD) and prednisone were prepared as 1:1:1 ratios using different blending sequences. ITMC was used tomonitor the thermal activity of the powder mixtures before and after each blending process. Differential Scaning Calorimetry (DSC) and X-ray powder diffraction (XRPD) were performed on all final powder mixtures. Final powder mixtures were used to prepare tablets with 10 mg prednisone content and dissolution tests were performed on all tablet formulations.
Results: Powder mixtures had different thermal activity depending on the blending sequences of the ingredients. All mixtures prepared by mixing prednisone with DCPD in the first stage were associated with relatively fast and significant heat exchange. In contrast, mixing prednisone with MCC in the fist step resulted in slower heat exchange. DSC showed that powder mixtures that showed hight thermal activity using ITMC were associated with the appearance of extra DSC peaks and their dissolution was generally slower compared to the other tablets.
Conclusion: This study showed that ITMC is a simple tool to observe solid-state reactions between excipients and prednisone according to blening process. Therefore, blending can be considered as a critical parameter in the tablet preparation. ITMC has the potential to be used in Quality by Design (QbD) approaches to optimize blending parameters for prednisone tablets.

83. Microcalorimetric Method to Assess Macrophage-Nanoparticle Interaction; Phagocytosis

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Purpose: This study evaluates the use of isothermal microcalorimetry (ITMC) to assess macrophage-nanoparticle interaction i.e., phagocytosis, using different nanoparticles (NPs) formulations.
Methods: Four different formulations of NPs were prepared as following; non-coated poly (isobutyl cyanoacrylate) (PIBCA), polysorbate 80-coated PIBCA, gelatin and mannosylated gelatin NPs. Changes in NP formulations aimed to either enhance or decrease NPs phagocytosis. Alveolar macrophages (MH-S) were culture on special cell-culture glass slabs and inserted in the ITMC channel. The thermal activity of macrophages alone and after titration 100 µl of NPs suspension, using a special Hamilton syringe, was recorded. The affinity constant of each one of previously mentioned NPs formulations towards macrophages were calculated using the total heat exchange recorded, NPs' concentration and macrophages' count. Control experiments were performed using cytochalasin B (Cyto B) as a known phagocytosis inhibitor.
Results: Macrophages alone showed a thermal activity profile consisted of 2 phases, ascending and descending. The total heat exchange recoded for macrophage alone over 100 hours was 9.84 ± 2.3 (J). After NPs titration, the total thermal activity, produced by macrophages, changed according to NP formulation. Mannosylated gelatin NPs were associated with the highest heat exchange and, consequently, the highest affinity constant, whereas the least was associated with polysorbate 80-coated NPs. The fact that Cyto B, as a known phagocytosis inhibitor, inhibited macrophages' response to NPs proved the connection between the thermal activity recorded and NP phagocytosis.
Conclusion: ITMC is a valuable tool to monitor biological and cellular process such as phagocytosis. Moreover, ITMC provides a better understanding of phagocytosis and its different phases, which is essential to develop future colloidal systems that either aim to target macrophages or evade them.

84. Impact of the Harmonized Specifications on the Performance of the Disintegration Test Introduction

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Purpose: USP chapter <701> was recently harmonized under ICH. No data exist which describes the impact of the new specifications on the performance of the disintegration test. The Aim of this study was to systematically investigate how beaker sizes, basket assembly, use of disks and the nature of immersion medium impact the disintegration of different dietary supplements.
Method: The disintegration times were determined for seven commercial tablets and capsule products. *Boswellia serrata*, *Cinnamon*, *Ester-C*, *Oyestercal* and *Glucosamine* were the tablet formulations and *Chasteberry* and *Zinc* were capsules products, which were investigated. A disintegration tester (model ED-2L, Electrolab, Betatek) consisted of two stations; each was used with Apparatus A USP chapter <701> or Apparatus B as described in USP chapter <2040>. The small beaker (SB) had a nominal volume of 1000 mL with an inside diameter of 101 ±1 mm, the large beaker (LB) had a nominal volume of 1,5 L and an inside diameter of 114 ±1 mm. The data were analyzed using two-way ANOVA for the following factors: beaker size (small, and big) and equipment (App A with disk, App A without disk, App B with disk, App B without disk).
Result: Two tablet products (*Boswellia and Oystercal*) were not sensitive to any changes in the test conditions or equipment configurations. A third product (*glucosamine tablets*) only showed a partial impact of the beaker size and the equipment used on the disintegration time when no disks were used. The other tablets *(Cinnamon and Ester-C*) showed a clear impact on the disintegration time when disks were used. The results showed that these tablet products might pass or fail current USP disintegration requirements depending on which

equipment configuration was chosen. Similar results were obtained for the two investigated capsule formulations. *Chasteberry* capsules failed to pass current USP disintegration requirements if the LB was used but past the disintegration requirements when the SB was used. The Zinc capsules, which had a cellulose-based shell, were mostly influenced in their disintegration times if sodium instead of a potassium buffer was used as immersion medium.

Conclusion: The results demonstrate that the current harmonized ICH specifications for the disintegration test are insufficient to make the disintegration test to a reliable performance test for dietary supplements. The impact of the current specifications on drug products needs to be investigated especially if the disintegration test is intended as performance test in a QbD approach.

85. The Rupture Test as a Performance Test for Soft Shell Capsules

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Purpose: USP chapter <2040> intended for dietary supplements introduced a rupture test for the performance testing of soft shell capsules. Traditionally, the disintegration test was used for determining the disintegration time of all oral dosage forms. The aim of this investigation was to investigate differences between the rupture test and the disintegration test for soft shell capsules.

Method: Five different soft shell capsules were chosen based on their filling content and manipulated to simulate a production deficiency. The study design compared capsules as received with capsules which were manipulated to simulate a production deficiency. The capsules were incubated at room temperature and at 40°C and the tests were repeated after 2 weeks. At each time point twelve capsules of each product were tested using the Rupture and the disintegration test; six capsules were tested un-manipulated while the other six capsules were manipulated at the beginning of the study by coating them with the liquid content of another capsule. Rupture and disintegration time were recorded as dependent variable in each experiment. The data were analysed using ANOVA.

Result: Disintegration is defined by USP as "that state in which any residue of a unit, except fragments of insoluble coatings or capsule shells parts, remain on the screen of the test apparatus or adhering to the lower surface of the disk, if used, are a soft mass having no palpably firm core" (USP 32, chapter *<701>, 2009)*. According to this definition the rupture of a soft shell capsule can be seen as full filling the disintegration criteria of the disintegration test if the capsule content is a semi-solid or liquid. Statistical analysis showed no significant differences between the disintegration and the rupture tests. However, the only statistically noticeable difference was that the rupture test reached the defined endpoint faster than the disintegration test.

Conclusion: Soft Shell capsules which are subject to a Quality by Design approach should be tested with both methods to determine which test is the most appropriate test for the specific product.

86. Formulation of Curcumin Loaded Nanoparticles for Improving Brain Targeting to Treat Alzheimer's Disease

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Purpose: Alzheimer's disease (AD) is one of the common and progressive neurodegenerative diseases. Deposition of amyloid β plaque and associated neuroinflammation are the major characteristic events of AD. The reactive oxygen species (ROS) as well as the activated microglial cells are reported to contribute to neuronal loss where as nuclear factor kB and apolipoprotein E are observed to participate in inflammatory process of AD. The current drugs approved by FDA provide only symptomatic relief in AD. In order to have a broad spectrum of activity, some natural products are also being explored and investigated. Curcumin, a yellow colored polyphenol present in the spice turmeric (Curcuma longa), has been reported to have antioxidant, anti-inflammatory and neurodegenerative effects. However, curcumin is sparingly soluble in water, which is one of the reasons for its poor absorption and low bioavailability, thus limiting its clinical application. In the present study we have formulated curcumin loaded nanoparticles. The nanotechnology based delivery system is aimed at targeting the drug to the brain for treating AD besides providing a sustained

release of the drug from the formulation thereby increasing its bioavailability.

Methods: 1. Formulation of Placebo and Drug Loaded Nanoparticles: The nanoparticles were prepared using solvent evaporation technique using PLGA as the release rate controlling polymer. 2. Particle size and size distribution: Once prepared, PLGA nanoparticules size and size distribution were analyzed using NanoS90 (Malvern instruments) with a DTS Nano software. 3. *In vitro* cytotoxicity study: Nanoparticles toxicity was then performed on a human neuroblastoma SK-N-SH cells. After treatment the cells were incubated for 24 hours after which the cell death was measured with LDH test and the cell survival were estimated using Resazurin test.

Results: The placebo and curcumin loaded PLGA nanoparticles were successfully prepared. The placebo formulations had a size between 83nm-86nm whereas the size of drug loaded formulations was between 88nm-101nm. In all measurements the Poly Dispersity index denoted by PDI was within the permissible range. As concluded from the results of in vitro toxicity tests, no cytotoxicity was observed after treatment with placebo and drug loaded nanoparticles.

Conclusions: The placebo and curcumin loaded PLGA nanoparticles were successfully prepared. No cytotoxicity was observed after treatment with placebo and curcumin loaded formulations.

87. Self-Assembling Rosette Nanotubes as a Novel Delivery System for siRNA

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Purpose: Small interfering RNA (siRNA) is a Nobel-Prize winning technology that has shown therapeutic potentials in animal models. However, several drawbacks preclude the direct application of siRNA in clinical practice such as instability in serum, poor cellular permeability, unfavorable pharmacokinetic and biodistribution profiles, and possible off-target effects. Therefore, we propose rosette nanotubes (RNTs) as a mean to optimize siRNA delivery strategy. RNTs are superstructures that are based on the entropy-driven self-assembly of a synthetic self-complementary guanine-cytosine (G∧C) motif. This unique property allowed RNTs to exhibit biological significance such as enhancement of osteoblast adhesion properties, improvement of titanium vascular stent applications, and induction of inflammation and apoptosis in human lung adenocarcinoma cells. Also, the relatively low cytotoxicity profile of these RNTs was attractive for consideration as siRNA delivery system.

Methods: Cationic RNTs are generated by functionalization of G∧C motifs with 2, 3, or 4 L-lysine residues to a twin G∧C motif (K-RNTs). siRNA were incubated with increasing weight ratios with K-RNT for 45 min at 37^{o}C. The degree of electrostatic interaction between siRNA and each K-RNT ratio was determined by agarose gel retardation assay. Optical properties were studied by UV-Vis spectroscopy. Surface morphology was assessed by SEM.

Results: The degree of siRNA binding was correlated with the cationic density and ratio of each K-RNT type. Fewer amounts were required from higher cationic density K-RNT to completely interact with siRNA and prevent its migration in response to the electric flied. UV-Vis analysis indicates changes in the optical properties of K-RNT and siRNA only after the complete interaction between both entities. Bathochromic shifts were seen with K_3-RNT/siRNA at weight ratio of (4:1), which was the only ratio that allowed complete interaction. K_4-RNT/siRNA showed bathochromic shift at (2:1) ratio, where complete interaction occurred. This was lost in K_4-RNT/siRNA (4:1) ratio due to excess un-reacted K-RNT in spite of the complete interaction seen by gel retardation assay. SEM pictures showed that the presence of siRNA induces K-RNTs aggregation, which is not seen in the free K-RNTs. With K_4-RNT/siRNA, these aggregates further coagulated into spherical structures of 100-300 nm probably due to interfacial tension.

Conclusion: We were able to develop a biocombatable delivery system for siRNA based on nanotechnological principles. Such delivery strategy is currently being tested for biological activities in cell cultures and lab animals.

88. Controlled Release of Alendronate from Nanocomposite Films for Periodontal Application

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Purpose: The current method for the treatment of periodontal disease is debridement followed by the placement of a barrier film over damaged bone and under the gum in order to promote bone regrowth around the base of the tooth. However along with the barrier film, material such as bone graft or hydroxyapatite is often placed in the debrided void to promote bone growth. Bisphosphonate drugs such as alendronate are commonly used to promote bone growth. Previous studies have described the effective encapsulation of alendronate in poly(lactic-co-glycolic acid) (PLGA) periodontal barrier films. However, a large burst phase release of alendronate from PLGA films was observed and found to be toxic for osteoblast cells. Therefore, the objective of this study was to develop a biodegradable barrier film that reduced the initial burst release of alendronate and delivered the drug in a linear fashion for at least one month.
Methods: Alendronate was encapsulated in nanoparticulate clay (known as layered double hydroxide) particles, forming a nanoclay-alendronate complex. This complex was incorporated into a film composed of PLGA (85:15)**.** The plasticizing and porosity-enhancing agent methoxy poly(ethylene glycol) (MePEG) was also blended into the composition. The films were cast by solvent evaporation and characterized for drug encapsulation, swelling, elasticity and drug release properties. The time-course of changes in elasticity and swelling following incubation in PBS were determined using thermo mechanical analysis (TMA). Drug encapsulation and release was measured using HPLC determinations.
Results: Alendronate was encapsulated into nanoclays with high efficiency (~33% w/w drug/clay) and the drug released into PBS over a four day period. The release profile of alendronate from the nanocomposite PLGA films was characterized by a neglible burst phase of release (<4% of encapsulated drug) followed by almost linear release over four weeks. The addition of MePEG successfully plasticized PLGA to make a flexible film and did not have any unwanted effect on the rate of alendronate release from the films. The films containing 15% (w/w) MePEG were found to be elastic by TMA but formed semi rigid structures within one hour of incubation in PBS (suitable for surgical applications).
Conclusions: These studies demonstrate the effective use of nanoclays for the controlled release of alendronate. The nanoclay-drug complexes were successfully dispersed into PLGA films. The addition of porosity enhancers allow the nano-composite films to be stretched over the base of the tooth (but stiffen and swell to seal the debrided pocket), followed by optimal release of alendronate to potentially improve bone growth. Further research is ongoing to evaluate osteoblast cell proliferation on these films.

89. Improvement of Extraction Efficiency of Unbound Radiolabeled Compounds in Microsomal Bioactivation and Binding Studies

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Purpose: Whether or not bioactivation and covalent binding play a role in drug toxicity is controversial. The first approach for assessing binding potential is microsomal studies with a radioisotope-labeled test article in comparison to benchmark levels. The present study tested the durability of this approach and identified improvements.
Methods: To assess robustness, an experimental substrate (^{14}C-Compound A) and diclofenac [carboxyl-^{14}C] were incubated with RLM at 37°C for 60 min with or without an NADPH-generating system. Incubation was terminated by adding acetonitrile. Various solvent extraction protocols were evaluated for the removal of unbound ^{14}C-radioactivity in the precipitated RLM pellet, and the remaining ^{14}C-radioactivity was measured by liquid scintillation counting (LSC).
Results: Using standard wash procedures, the NADPH-dependent non-extractable radioactivity obtained was 308, 512 and 1278 pmol/mg protein from incubations of ^{14}C-Compound A at 1, 10, and 50 μM, respectively. However, following an alternative wash procedure of the precipitate, radioactivity was reduced by 75% to 302 pmol/mg

protein from incubation of ^{14}C-Compound A at 50 µM. For ^{14}C-diclofenac incubated at 10 µM, the NADPH-dependent non-extractable radioactivity was equivalent to 33 pmol/mg using the standard wash procedure, but was reduced to 6.1 pmol/mg following the alternative wash procedure. When RLM pellets were digested with trypsin, HPLC on-line Stop-Flow™ radiometric analysis did not detect radioactivity. When HPLC fractions were analyzed by LSC, radioactivity above background was observed in fractions collected before, near, and after the retention time of Compound A.

Conclusion: Solvent wash procedures, trypsin digestion and measurement of radioactivity in HPLC fractions greatly impacted the extraction efficiency of unbound radioactivity from RLM pellets and thus the evaluation of binding against proposed benchmark levels.

90. Development of a Novel Micelle Formulation and Pharmacometrics of the mTor Inhibitor, Deforolimus

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Purpose: To develop a LC/MS method of analysis for deforolimus; develop an intravenous (IV) micellar formulation of deforolimus for administration to rats; delineate the pharmacokinetics of deforolimus; and examine the pharmacologic activity of deforolimus.

Methods: A LC/MS method was used utilizing a C_{18}(2) column with a mobile phase of methanol, water, and formic acid (90:10:0.1, v/v/v/) modified with 2mM ammonium acetate at a flow rate of 0.50 mL/min. Detection was achieved using positive selective ion monitoring at m/z 1012.60 for deforolimus. A polymer (1,2-distearoyl-*sn*-glycero-3-phosphoethanolamine-N-[methoxy(polyethylene glycol)-2000] (ammonium salt)) was used to solubilize deforolimus. The nanomicelles or an ethanol/PEG 400 solution of deforolimus was administered IV to cannulated male Sprague-Dawley rats at 10 mg/kg. Serum and urine samples were collected from 0-72h post-dose. Atomic absorption spectrometry in the flame ionization mode was used to monitor the fluctuation in sodium and potassium concentrations (0.1-4 µg/mL) in urine at 24h. Pharmacological activity of deforolimus was evaluated by studying the inhibitory effects of deforolimus on cancer cell proliferation (HT-29, A375, and HepG2), adipogenesis (3T3-L1), and cyclooxygenase (COX) -1 and -2 *in vitro* over the concentration range of 0-100 µg/mL.

Results: A novel LC/MS method for the detection of deforolimus was developed with observed linearity between 0.05-10 µg/mL. The micellar formulation increased deforolimus aqueous solubility by ~40 times with a suitable particle size for IV administration at ~33 nm. Pharmacokinetic parameter differences between the micellar and ethanol/PEG 400 formulations were evident. The micelle formulation had a 12.1 fold increase in $t_{1/2}$, a 3.5 fold increase in AUC, and a 2.3 fold decrease in CL_t. Renal potassium excretion was not affected by IV administration of deforolimus in either formulation, but micellar formulation did decrease renal sodium levels in rat urine at 24 h. Deforolimus was able to inhibit cell proliferation, reduce adipogenic activity, and inhibit COX-1 and -2.

Conclusions: A sensitive, reproducible, and accurate LC/MS method was developed for the detection of deforolimus. A micellar formulation suitable for IV administration was developed that demonstrated attenuation of $t_{1/2}$, AUC, and CL_t in comparison to controls. Deforolimus possesses anti-cancer, COX inhibitory, and anti-adipogenic properties.

91. Bone-targeting Salmon Calcitonin Analogue: Synthesis, Characterization and *in vivo* Evaluation

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Purpose: Salmon calcitonin (sCT), indicated in the treatment of Osteoporosis, Paget's disease and hypercalcaemia of malignancy, elicits its antiresorptive effect by acting upon Calcitonin receptors (CTRs) on bone-resorbing osteoclasts (OC). However, CTRs are also widely expressed in non-skeletal tissues like kidney, brain, and lung, and the competitive uptake of available sCT amongst CTRs likely reduces sCT availability for bone resident OC, particularly if the drug is not specifically targeted to bone. Hence, the objective of this study was to synthesize and characterize a bone

targeting sCT analogue, and to determine whether the bioactivity of sCT was retained after conjugation.
Methods: sCT was reacted with sulfosuccinimidyl-4-[N-maleimidomethyl] cyclohexane-1-carboxylate (SMCC) in presence of triethylamine (TEA) to generate sCT-SMCC. Effect of reaction time, sulfo-SMCC and TEA concentrations was determined by matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF) analysis. sCT-SMCC was then reacted with thiol bisphosphonate (BP). sCT-BP conjugates were purified by dialysis, assayed for sCT, and characterized by MALDI-TOF and Tris-Tricine SDS-PAGE. The effect of structural alteration on sCT secondary structure was examined by circular dichroism and conjugates were evaluated for *in vitro* bone mineral affinity using a binding assay for bone hydroxyapatite and several other calcium salts. Conjugated CT epitope binding specificity was determined using ELISA, by reacting conjugates with calcium phosphate coated plates and detecting the bound sCT using anti-CT antibody. Cytotoxicity of the conjugates was evaluated in OC precursor RAW 264.7 cells and sCT bioactivity and CTR binding potential evaluated by intracellular cAMP stimulation assay in human T47D breast cancer cells. The *in vivo* efficacy of conjugates was evaluated by determining hypocalcaemic and hypophosphatemic effects after sub-cu administration in normal rats.
Results: Conjugation of BP to sCT altered its secondary structure into more stable and desirable alpha helical form without altering its receptor binding specificity. This sCT analogue exhibited significantly greater affinity and specificity for bone mineral over unmodified sCT, retained strong sCT bioactivity, was non-toxic to bone marrow cells and exhibited comparable hypocalcaemic and hypophosphatemic effect to that of sCT.
Conclusion: Our BP-conjugated sCT analogue exhibits significant bone mineral affinity and specificity. It holds the promise of facilitating the delivery of sCT preferentially to skeletal bony tissues, thereby increasing its local concentration to bone surfaces, whilst maintaining sCT bioactivity.

92. Preclinical Evaluation of an Oral Micellar Formulation of SN38

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Purpose: SN38, the active metabolite of CPT-11 (irinotecan), is a potent cytotoxic agent. Due to its low aqueous solubility, development of an oral administration has so far been precluded. To address this formulation challenge, we used our library of block copolymers of polyethyleneglycol-polymethacrylate (PEG-PMA) to prepare pH-sensitive micellar formulations of SN38 for oral administration. The present study evaluated in vitro permeability and the tolerability and efficacy of this new formulation after oral administration to Swiss nude mice bearing human tumors.
Methods: Permeability studies were performed *in vitro* using Caco-2 monolayers cultivated for 21 days. Oral single dose (MTD) and repeated dose (MTTD) tolerability studies were conducted in Swiss nude mice. For MTTD evaluations, the formulation was administered orally to tumor bearing animals (Q1Dx 5) x 2 weeks. Efficacy studies were performed in Swiss nude mice (n = 12/group) bearing human HCT-116 colon carcinoma or human Mia-PaCa-2 pancreatic carcinoma xenografts. SN38 micellar formulation was administered orally at 12.5, 25, 50 and 75 mg/kg/d qd x 5d x 2 wk q21d for at least 2 cycles. CPT-11 was administered IV at 50 mg/kg q7d x 2 wk q21d for at least 2 cycles. Vehicle control groups using the same regimen as oral micellar SN38 were also evaluated. Body weights and tumour volumes were monitored three times per week.
Results: Transport of SN38 released from micellar formulation (10mg/L) was increased approximately 250% compared to SN38 dissolved in DMSO. Orally administered micellar SN38 was well tolerated after a single dose (> 200 mg/kg) and repeated dose regimens (between 50 and 100 mg/kg/d. Micellar SN38 was also well tolerated after oral administration into colon and pancreatic xenografts. In HCT-116 xenografts, significant reductions in relative tumour growth were observed after 5 and 12 days of treatment with 50 and 75 mg/kg/d respectively, compared to vehicle controls ($p < 0.05$). After 2 cycles of treatment, the mean relative tumor volumes in the micellar SN38 treated mice at 50 and 75 mg/kg/d were similar to mice

administered CPT-11 ($P > 0.5$). In the case of Mia-PaCa-2, significant reductions in relative tumour growth were observed after 11 days administration of micellar SN38 at 50 mg/kg/d compared to vehicle controls ($p < 0.05$).

Conclusion: The efficacy of micellar SN38 in xenograft models of colon and pancreatic cancer was demonstrated. These results suggest that oral micellar SN38 is a promising agent and should be evaluated in clinical trials.

93. Characterization of Nano-carriers Formed from Self Assembly of Methoxy Poly(ethylene oxide)-*block*-poly(α-benzyl carboxylate-ε-caprolactone) for the Solubilization and *in vivo* Delivery of Valspodar

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Purpose: To investigate the potential of polymeric nano-carriers based on methoxy poly(ethylene oxide)-*block*-poly(α-benzyl carboxylate-ε-caprolactone) (PEO-*b*-PBCL) for the solubilization and delivery of P-glycoprotein (p-gp) inhibitor, valspodar.

Methods: Three PEO-*b*-PBCL block copolymers having identical methoxy PEO molecular weights (5 kDa) and different molecular weights of PBCL (8, 15, and 24 kDa) were synthesized and assembled into polymeric nano-carrires using a co-solvent evaporation method. Prepared nano-carriers were characterized for their average diameter, morphology, thermodynamic stability, core viscosity, and drug encapsulation. Valspodar was physically encapsulated in PEO-*b*-PBCL nano-carriers by addition of drug in the organic co-solvent during the self assembly process. The unbound fraction (f_u) of valspodar for the different nano-carriers was determined in rat plasma. The pharmacokinetic profile of each formulation was assessed in rats. Valspodar concentrations were analyzed using an LC/MS method. Non-compartmental approach was used to estimate the pharmacokinetic parameters.

Results: All the synthesized PEO-*b*-PBCL block copolymers self assembled at low concentrations in the range of 23-62 *n*M. Assembly of prepared block copolymers led to the formation of nanostructures with average hydrodynamic diameters of 104, 95.5, and 74.1 nm for PEO-*b*-PBCL having PBCL blocks with molecular weights of 8, 15 and 24 kDa, repectively. The TEM studies revealed self-assembly of PEO-*b*-PBCL block copolymers to polymeric micelles except for PEO_{5000}-*b*-$PBCL_{15000}$ and PEO_{5000}-*b*-$PBCL_{24000}$, which have shown a subpopulation consisting of polymeric vesicles. Valspodar, which is practically insoluble in water, achieved high loading in all the three nanostructures reaching aqueous solubility of 2.0, 1.4 and 1.7 mg/mL in the presence of PEO_{5000}-*b*-$PBCL_{8000}$, PEO_{5000}-*b*-$PBCL_{15000}$ and PEO_{5000}-*b*-$PBCL_{24000}$ nano-carriers, respectively. Moreover, preliminary pharmacokinetic studies in rats showed that PEO-PBCL nano-carriers were able to increase the half-life of valspodar by decreasing its clearance compared to control formulation containing Cremophor EL and ethanol.

Conclusion: Our results point to a great potential for PEO-*b*-PBCL nano-carriers for efficient solubilization and delivery of valspodar.

94. Tumor Targeted Polymeric Micelles for Co-Delivery of Sirna and Anticancer Drugs: A New Strategy for Chemo-Sensitization of Resistant Tumors

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Purpose: The purpose of this study was to develop polymeric micelles for efficient co-delivery of siRNA and anticancer drugs.

Methods: Acetal and TAT modified poly(ethylene oxide)-*block*-poly(ε-caprolactone) (PEO-*b*-PCL) copolymers containing cationic spermine (SP) on their PCL block (acetal- or TAT-PEO-*b*-P(CL-*g*-SP)) as well as RGD4C-PEO-*b*-PCL copolymers containing hydrazone-bound doxorubicin (DOX) on their PCL block (RGD4C-PEO-*b*-P(CL-Hyd-DOX)) were synthesized. Multifunctional micelles were self-assembled from a mixture of these polymers (1:1:4, molar ratio). In the final micellar core structure, the negatively charged siRNA was condensed by polycations, while DOX was chemically conjugated by pH-sensitive linkages. The micellar shell was functionalized with two ligands, i.e. integrin αvβ3-targeted RGD (RGD4C) and cell penetration peptide (TAT) for cancer targeting and cell entry, respectively. The formation of mixed

micelles was confirmed by two-color flow cytometry analysis and characterized by AFM. Cellular uptake and distribution of DOX and siRNA was evaluated in αvβ3+/P-glycoprotein (P-gp)+ MDA435/LCC6 resistant cancer cells. Finally, the effect of multifunctional micelles containing DOX and mdr1 siRNA on the cytoxicity of DOX in MDA435/LCC6 resistant cancer cells was evelauated.

Results: The multifunctional micelles with a particle size of ~ 100 nm were successfully prepared. RGD and TAT modified micelles (RGD/TAT-micelles) showed significantly higher cellular uptake of siRNA and DOX compared to micelles modified with single peptide (RGD or TAT) on their surface. Confocal microscopy revealed efficient endosome escape of DOX and siRNA for RGD/TAT-micelles. The multifunctional RGD/TAT micelles containing complexed mdr1 siRNA and conjugated DOX significantly increased DOX accumulation in P-gp overexpressing MDA435/LCC6 resistant cells and led to the reversal of DOX resistance in those cells.

Conclusions: The developed multifunctional micelles are promissing for efficient simultaneous delivery of anticancer drugs and therapeutic siRNA against expression of oncogenes. Integration of multiple therapeutic moieties into the same nanoparticle may be used as an efficient strategy for chemo-sensitization of resistant tumor cell phenotypes.

Pharmaceutical and Analytical Chemistry

95. The Evaluation of a Mouse Dried Blood Spot Serial Sampling Technique to Provide Blood PK Data during Pharmacology Studies

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Purpose: Traditional pharmacokinetic (PK) studies in mice usually require a significant number of test animals in a composite sparse sampling design to provide adequate sample volumes and time pointsfor measurement. The dried blood spot (DBS) sampling technique has recently gained popularity owing to the small blood sampling volumes offered by this approach, which potentially enables the use of fewer test animals in a serial sampling design to produce PK data with higher data quality and at a lower cost. This study was designed to evaluate potential differences in data quality of *in vivo* PK of BRI-101, a proprietary drug candidate, based on sparse-sampling and serial DBS sampling from parallel groups of mice following a single subcutaneous administration.

Methods: BRI-101 was provided by a commercial study sponsor and a single subcutaneous dose was administered to two groups of female mice following by either sparse sampling of plasma or serial DBS sampling of whole blood with the use of GE Whatman DMPK™ sampling card. Sparse-sampling was performed as a terminal blood draw from each mouse with the use of K_2EDTA anticoagulant using three mice per sampling time. Serial DBS sampling was performed based on 20 µL whole blood at each time point throughout the PK time-course from three mice. An LC/MS/MS assay was established for the assay of BRI-101 in plasma and in DBS PK samples and the performance of the LC/MS/MS assay of DBS samples will be presented.

Results: The recovery of BRI-101 from DBS samples 1, 5 and 40 µg/mL was evaluated and observed to be consistent and reproducible at 70%, 68% and 65%, respectively. The LC/MS/MS assay quantitation range was established over a range of 500 ng/mL to 50 µg/mL, with a lower limit of quantitation established at 500 ng/mL based on 20 µL whole blood DBS sampling. The plasma PK profile of BRI-101 in mouse obtained from conventional sparse-sampling and from serial DBS sampling will be presented and discussed.

Conclusion: The serial DBS-sampling technique offers less variable PK data compared with sparse-sampling PK data confounded by variations between animals. This serial DBS sampling approach provides an improvement *in vivo* PK data quality at reduced cost and offers an opportunity to generate valuable PK data during conventional xenograph, transgenic and other similar mouse pharmacology efficacy studies.

96. A Sensitive HPLC Assay of Glucosamine in Biological Samples

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Purpose: The reported methods for glucosamine determination in plasma were either complicated and expensive or showing indistinct chromatograms. The aim of this study was to develop a simple, inexpensive, sensitive and precise analytical method for determination of glucosamine in different biological fluids which can be utilized for better understanding of glucosamine pharmacokinetics.
Methods: Aliquots of 0.1 ml human plasma, rat plasma, urine, fecal extract, intestinal fluid, and intestinal homogenate were spiked with mannosamine HCl (internal standard); proteins precipitated with acetontrile; the clear layer was derivatized with 9-fluorenylmethyl chloroformate (8 mM/acetonitrile) in presence of borate buffer 0.2M at 30^{o} C for 30 min. The excess dervatizing agent was removed with amantadine HCl (300 mM in Acetonitril-water 1:1). Chromatographic separation obtained on Phenomenex C18 (100mm X 4.6 mm, id 3μm) reversed phase column, using 0.1% acetic acid/acetoniltril gradient mobile phase (77%:23% →10%: 90%) at 1 mL/min flow rate. Detection of glucosamine obtained at excitation and emission wavelengths of 263 and 315 nm, respectively.
Results: The assay was linear over the range of 0.05-20 mg/L with a typical correlation coefficient of 0.999. The lower limit of quantification was 50 ng/mL with intera-day and inter-day coefficient of variation of <15%. The recovery for glucosamine and mannosamine was found to be 82% and 84%, respectively.
Conclusion: We were able to improve glucosamine assay by fluorescence detection and present a rapid, simple, sensitive and precise method. The method is suitable for studying glucosamine pharmacokinetics following therapeutically low doses.
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Pharmacokinetics and Pharmacodynamics

97. Hemodynamic Response to Exercise in Normotensive SD Rats and SHR *in vivo*

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Purpose: To study the hemodynamic response to treadmill exercise in normotensive SD rats and SHR *in vivo*. **Methods:** Sprague Dawley (SD) rats and spontaneously hypertensive rats (SHR) weighing between 250 and 300g were used. Each rat was acclimatized to the Carleton Animal Care Centre and free access to food and water for at 48 hours before experiment. Each rat was exercised on a research treadmill (Model Exer-4, Columbus Instruments International Corp., Ohio, USA) for 15 minutes at a treadmill speed of 10 m/min and 5% grade. Each rat was returned to a restrainer after exercise, and hemodynamic recording (SBP, DBP, and HR) were collected throughout the experiment for up to 6 hrs using a TruWave® disposable pressure transducer (Model PX601, Edwards Lifesciences Canada, Inc., Mississauga, ON, Canada) coupled to a Siemens hemodynamic monitor (Sirecust 400) and chart recorder (Siredoc) (Erlangen, FRG). Hemodynamic data between the SD rats and SHR were compared using ANOVA and *t*-test and difference considered significant at $p < 0.05$.
Results: The baseline SBP and DBP were significantly higher in the SHR (SBP 199 ± 25 vs 124 ± 14 mmHg; DBP (165 ± 17 vs 116 ± 15 mmHg), but there was no difference in the HR between the SD rats and SHR (409 ± 53 vs 431 ± 35 bpm). A 15-min exercise under the described condition significantly increased mean SBP (+31%), DBP (+18%) and HR (+13%) in SD rats, but only the HR (+12%) was significantly increased in the SHR. At the end of the 6-hr experiment, SBP and DBP fell significantly below the baseline in the SHR by -23 and -36%, respectively; only the DBP fell by -22%. The HR was relatively unaltered after exercise ($p > 0.05$) in both SD rats and SHR.
Conclusion: SHR are more resistant to BP increased induced by exercise, and have a more profound post

exercise hypotension (Supported in part by CIHR, Nova Scotia Health Research Foundation and Dalhousie Pharmacy Endowment Foundation).

98. Effect of Postprandial Hypertriglyceridemia on the Pharmacokinetics and Blood Brain Barrier Penetration of Clozapine and Norclozapine in Rats

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Purpose: Clozapine is an atypical antipsychotic lipophilic agent that is used for treatment of resistant schizophrenia. Clozapine treatment is associated with multiple adverse effects, including hypertriglyceridemia. There is a long-term discussion in the literature concerning the possible link between the improved efficacy of clozapine treatment and elevated plasma triglyceride levels, but no mechanistic studies have been performed to date. Alterations in pharmacokinetic profile and in blood-brain barrier (BBB) penetration were proposed as one of the possible reasons for increased pharmacological activity of clozapine in hypertriglyceridemic state. The aim of this work was to investigate whether the postprandial hypertriglyceridemia affects the pharmacokinetics and BBB penetration of clozapine and norclozapine.
Methods: Moderate or severe experimental hypertriglyceridemia in rats was induced by oral administration of different doses of peanut oil and clozapine and norclozapine were administered intravenously to hypertriglyceridemic and normolipidemic animals to obtain plasma-concentration time profile and to calculate pharmacokinetic parameters. To assess the BBB penetration of clozapine and norclozapine, clozapine was administered intraperitoneally and the concentrations of clozapine and norclozapine were assessed in plasma and brain of hypertriglyceridemic and normolipidemic animals one hour following the administration. The levels of clozapine and norclozapine were determined by means of HPLC-UV and hypertriglyceridemia was monitored using an enzymatic kit.
Results: Statistically significant hypertriglyceridemia was induced in both, moderate and severe hypertriglyceridemic treatment groups as well as in hypertriglyceridemic animals in BBB penetration study. Moderately increased clearance of clozapine was found in hypertriglyceridemic animals compared to control group. Hypertiglyceridemia did not affect the penetration of compounds across the BBB.
Conclusion: Taken together, the results do not support the hypothesis that hypertriglyceridemia improves the effect of clozapine by altered pharmacokinetics of clozapine and norclozapine and their increased penetration across the BBB.

99. Characterization of P-glycoprotein Transport in a Novel Human Proximal Tubule Cell Line

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Objective: P-glycoprotein (P-gp), located in the apical membrane of kidney proximal tubule cells, is a drug efflux transporter that mediates drug elimination from the body. The primary objective was to characterize P-gp function in a novel human kidney proximal tubule (PT) cell line. Following validation, the PT cell model will be used to examine the effects of inflammation and infection on P-gp mediated transport and nephrotoxicity of immunosuppressant drugs.
Methods: We used quantitative PCR and western blot to assess the quantity of mRNA and protein expression of P-gp in the PT cell line. Once these levels were established, a cellular accumulation assay using the fluorescent P-gp substrate rhodamine 123 was performed to determine the functional P-gp transport.
Results: PT cells are a novel proximal tubule cell line isolated from an anonymous renal transplant patient at the IWK Health Center in Halifax NS. First we determined if the cells expressed *ABCB1*, the gene that encodes P-gp. The levels of *ABCB1* mRNA were higher than basal levels in a control immortalized human kidney (HK2) cell line. Consistent with the amount of mRNA, P-gp protein

expression was found to be similar to that of a breast cancer cell line (MFC7-TX400) known to overexpress the protein. To determine if P-gp was functional, we evaluated the cellular accumulation of the fluorescent P-gp substrate rhodamine123 in the presence and absence of the P-gp inhibitors verapamil and cyclosporine A. When concurrently treated with either Pgp inhibitor, the steady-state level of rhodamine123 increased by approximately 2-fold. These findings are consistent with functional P-gp transport and blockade.

Conclusion: The high level of *ABCB1* mRNA and P-gp expression and function is consistent with a key characteristic of human proximal tubule cells and validates the model. In PT cells, initial results demonstrated a synergistic cytotoxic effect with cyclosporine A and the inflammatory mediator tumor necrosis factor-α. Moving forward we will investigate the hypothesis that this effect stems from enhanced cyclosporine A accumulation due to an inflammation mediated loss in P-gp function.

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100. Pharmacokinetics, and Pharmacodynamics and Liquid Chromatography Mass Spectrometry Assay Methodology of β-glucogallin and Gallic Acid

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Purpose: To develop a novel analytical method using HPLC/ESI/MS (high-pressure liquid chromatography electrospray ionization tandem mass spectrometry) for the simultaneous detection of β-glucogallin and gallic acid; characterize the pharmacokinetics of β-glucogallin and gallic acid after oral administration of β-glucogallin; determine possible pharmacological activity of β-glucogallin and gallic acid *in vitro.*

Methods: A novel HPLC/ESI/MS method was developed using a C_{18}(2) column, ultraviolet detection (UV) at 285nm in negative selective ion monitoring mode. The mobile phase consisted of a mixture of water, methanol, and formic acid (90:10:0.1, v/v/v), modified with 2mM of ammonium acetate, with a flow rate of 0.7 mL/min. Linear standard curves were established and applied to the pharmacokinetic study. β-glucogallin (100 mg/kg) was orally administered to male Sprague/Dawley rats; pharmacokinetic samples were collected over the duration of this study (120h) at predetermined times. Pharmacodynamic activity (anti-oxidant, anti-adipogenesis, and anti-proliferative activity and cyclooxygenase (COX) -1 and -2, and tumor necrosis factor alpha (TNF-alpha) inhibitory activity) was assayed using commercially available ELISA kits over the concentration range of 0-100 μg/mL.

Results: A method of analysis of β -glucogallin and gallic acid was developed with linearity obtained over the concentration range of 0.5-100 μg/mL using a 100 μL sample. This method was applied to the simultaneous detection of β-glucogallin and gallic acid disposition in urine. β-glucogallin and gallic acid demonstrate anti-oxidant and anti-adipogenic activity, conversely little to no anti-proliferative activity was evident. Inhibition of COX-1 and -2 was accomplished by both β-glucogallin and gallic acid, however, limited inhibition of TNF-alpha was demonstrated.

Conclusions: An analytical method for the simultaneous detection of β-glucogallin and gallic acid was developed. β-glucogallin undergoes rapid metabolism into gallic acid which is readily excreted in urine, although β-glucogallin, its glucuronide, and the gallic acid glucuronide are also excreted in urine. β-glucogallin and gallic acid possesses potential pharmacological benefits to modulate the inflammatory diseases.

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101. Characterization of the Pharmacokinetics and Pharmacological Activities of Gnetol

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Purpose: To develop and validate an analytical assay to quantify gnetol in biological fluids, to evaluate the pharmacokinetics of gnetol in a rodent model, and to examine the pharmacological activities of gnetol.

Methods: A HPLC method was utilized to quantify gnetol in rat serum and a LC/MS method was used to quantify gnetol in rat urine. For both methods, a C_{18} column with mobile phase of 35:65:0.04 (ACN: H_20: formic acid, v/v/v) at 0.4 ml/min was employed. Detection was absorbance at 305 nm or

negative SIM of m/z 243 for gnetol. Male Sprague-Dawley rats were cannulated and dosed either intravenously with gnetol in 1% DMSO in PEG 600 (10 mg/kg) or orally with gnetol in PEG 600 (100 mg/kg). Serum and urine samples were collected over a 120h period. Analgesia was assessed via the hot plate and tail flick methods in male NIH Swiss mice dosed subcutaneously with gnetol formulated in 2% Tween 80 in saline at 50 mg/kg. Gnetol's effect on cell viability in cancer cell lines (0-250 µg/mL) was assessed by the Alamar Blue method. Antioxidant capacity of gnetol (0-250 µg/mL) was measured by the ABTS method. Antioxidant capacity, COX-1 and-2 inhibition, and HDAC inhibition of gnetol were assessed via commercially available assay kits.

Results: The HPLC and LC/MS methods were successfully applied to gnetol pharmacokinetic studies. Serum and urine standard curves were linear over 0.1-100 µg/mL and 0.5-100 µg/mL, respectively. After oral and intravenous administration, gnetol was detected in both serum and urine as the parent compound and as a glucuronidated metabolite. Pretreatment of mice with gnetol was able to increase the latency period to response in both analgesia models. Gnetol decreased cell viability in all cancer cell lines in a concentration dependent manner. Gnetol possessed concentration dependent antioxidant capacity, and COX and HDAC inhibition activities.

Conclusions: Novel, sensitive HPLC and LC/MS methods were developed for gnetol detection in biological fluids. Pharmacokinetic studies of gnetol indicated it is orally bioavailable, rapidly undergoes Phase II metabolism, and excreted via renal and non-renal routes. Gnetol appears to possess analgesic activity *in vivo*. *In vitro* pharmacological activities include concentration dependent anti-cancer, antioxidant, COX inhibitory, and HDAC inhibitory activities.

102. The Effect of Hyperlipidemia on P-glycoprotein Activity in Porcine and Rat Renal Cell Line Models

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Purpose: Immunosuppressive agents such as cyclosporine A are frequently associated with nephrotoxicity. Hyperlipidemia appears to exacerbate this side effect by increasing the drug load inside the kidney. The underlying cause for increased drug uptake was assumed to be due to a possible inhibitory effect of lipoproteins on P-glycoprotein (Pgp) transporters. Therefore, our main objective was to investigate the effect of hyperlipidemia on Pgp activity.

Methods: Two renal epithelial cell line models of porcine (LLC-PK1) and rat (NRK-52E) origin were used in our studies. Since LLC-PK1 has little constitutive Pgp activity, Pgp expression and activity were induced by treatment with 25 µM rifampin for 7 days. LLC-PK1 cell line thus had two main groups, namely, non-rifampin and rifampin treated groups. On the other hand NRK-52E cells were used directly since they have significant levels of Pgp. The cell lines were cultured in 6- and 24-well plates for studying gene expression and activity, respectively. Thereafter, the cells were allocated into three subgroups. *Group 1*: treated with medium only, *group 2*: treated with 20% normolipidemic rat serum in media and *group 3*: treated with 20% hyperlipidemic rat serum in media. After 24 hours of exposure to rat serum, the media was replaced with serum-free media. Thereafter rhodamine-123 (Rh123, 10 µM) was added to media. Rh123 cellular uptake was assessed at 0.5, 1, 2, 4, 6 and 24 hours after incubation. Pgp gene expression and its activity were measured using real time polymerase chain reaction and fluormetric assay of Rh123 uptake inside the cells, respectively.

Results: In LLC-PK1 cells, rifampin resulted in significant induction in the Pgp gene expression (30%). Furthermore, rifampin treatment caused a significant decrease (~30%) in rhodamine uptake in each of medium only, normolipidemic serum and hyperlipidemic serum treated groups. Compared to normolipidemic serum, hyperlipidemic serum resulted in ~25% increased Rh123 uptake in each of non-rifampin treated LLC-PK1 cells, rifampin-treated LLC-PK1 cells and NRK-52E cells.

Conclusion: Elevated lipoprotein status was shown to decrease Pgp activity which may enhance the renal toxicity of immunosuppressive drugs which are substrates for Pgp.

103. In vivo Evaluation of Mucoadhesive Docetaxel for Intravesical Treatment of Nonmuscle-invasive Bladder Cancer

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Purpose: Current treatment options for nonmuscle-invasive bladder cancer following transurethral resection are of limited efficacy since up to 80% of patients develop recurrent tumors. Microtubules are one of the most successful targets in cancer therapy to date and the recent Phase I trial of intravesical docetaxel for treatment of nonmuscle-invasive bladder cancer refractory to BCG therapy has shown this to be a promising intravesical agent with minimal toxicity and no systemic absorption. The present work describes the development and *in vivo* evaluation of a mucoadhesive docetaxel formulation for intravesical bladder cancer therapy.
Methods: Mucoadhesive formulations based on hydrophobically derivatized hyperbranched polyglycerols (dHPGs) were synthesized and docetaxel was loaded into these by a solvent evaporation method. Four bladder cancer cell lines were treated with various concentrations of docetaxel formulations *in vitro*. Human KU7 bladder tumor 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 tumors were given a single intravesical instillation with PBS, Taxotere®(Docetaxel from Sanofi-Aventis) or mucoadhesive docetaxel.
Results: dHPGs are nanoparticles with hydrodynamic radii of less than 10nm and incorporation of docetaxel did not affect their size. The release profiles of docetaxel from these nanoparticles were characterized by a rapid release phase (55% drug release during the first 24 hours) followed by a slower sustained release phase. *In vitro*, all docetaxel formulations potently decrease bladder cancer proliferation. However, *in vivo*, mucoadhesive docetaxel was the most effective formulation to inhibit tumor growth in an orthotopic model of high-grade nonmuscle-invasive bladder cancer.
Conclusions: Our data show promising *in vivo* antitumor efficacy and provide preclinical proof-of-principle for the intravesical application of mucoadhesive docetaxel in the treatment of high-grade nonmuscle-invasive bladder cancer. Further research is warranted to evaluate its safety and efficacy in early phase clinical trials in patients refractory to standard therapy.

104. Pharmacokinetics and Biodistribution of Tramadol and its Metabolites in Rat

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Purpose: Tramadol hydrochloride is a centrally-acting analgesic used in the treatment of mild to moderate pain. The single dose pharmacokinetics of tramadol and its distribution in brain and other tissues in rats after intravenous administration were studied in this research.
Methods: The day before the experiments, the rats were anesthetized by intraperitoneal (i.p.) injection of a ketamine–xylazin cocktail and a polyethylene–silicone rubber cannula was implanted in the right jugular vein. On the day of the experiments, a 10 mg/kg dose of tramadol dissolved in a saline vehicle was injected intravenously to rats through the cannula. In one group at 10, 20, 30, 45, 60, 120, 180 min after administration, 0.5 ml blood sample was obtained. In the other group at 10 min post dose, the animals were anesthetized and a 1-ml blood sample was obtained via the cannula to pre-heparinized polypropylene microtubes. The animals were then immediately decapitated and the tissue samples including brain, heart, liver, small intestine (an approximately 3-cm piece of duodenum), spleen, kidney and testis were harvested. Tissue and plasma samples were analyzed after liquid-liquid extraction by ethylacetate. Determination was performed by HPLC using fluorescence detection [excitation wavelength (λex) 200 nm/ emission wavelength (λem) 301 nm]. The separation was performed on RP-18 column under isocratic elution. The mobile phase was a mixture of methanol:water (19:81) adjusted to pH 2.5 by phosphoric acid.
Results: The concentration of tramadol and its three

main metabolites O-desmethyltramadol (M1) and N-desmethyltramadol (M2) and N,O-didesmethyltramadol (M5) were determined in samples. The pharmacokinetics parameters were calculated for tramadol and its metabolites. A two compartment model was distinguished in intact rats for tramadol. Tramaol distribution and elimination T(1/2) were 7.5 and 49.5 minutes respectively. AUC(0–180) for tramadol, M1, M2 and M5 were 21096.4, 4189.5, 4199.8 and 3324.3 ng.ml/min respectively. The ratio of tramadol concentration in different tissues to plasma was calculated. The order of tramadol accumulation in different tissues was obtained as kidney, spleen, lung, intestine, testis, brain, heart and liver. None of above metabolites was detected in brain and testis considering LOD of 5 ng/ml.

Conclusion: All major metabolites of tramadol (seen in human) were detected in rat. However the distribution pattern of tramadol and metabolites are quite different in studied tissues.

AFPC
Poster Presentations
Day 2
Friday, June 4, 2010

Day 2

Basic Science

105. Construction of an Improved Gene Delivery Platform

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Background: Conventional vectors like circular plasmids pose immunostimulatory effects due to their prokaryotic backbone and safety risks due to integrate into the host genome, potentially result in cancer. In contrast, the frequency of viable integration events of linear vectors into host chromosome is likely lower than that of their ccc counterparts, since an integration event would interrupt the chromosome.
Objective: This study aims to apply the bacteriophages genetic system to design novel DNA vectors. Bacteriophages provide an invaluable pool of genetic encoding systems with widespread applications in molecular biology. The entrobacteriophages N15 and PY54 lysogenize their hosts as a linear plasmid with covalently closed ends (lcc plasmid). This conformation is conferred by the phage-encoded telomerase through a single cleaving-joining reaction of the target sequences. This system can be exploited to design an *in vivo* system for the generation of lcc mini-plasmids with higher safety platform that eliminates the parental prokaryotic backbone.
Methods: In this purpose, the *telN/tel* genes amplified from N15 and PY54 genomes were cloned separately downstream of a temperature-sensitive repressor, providing thermo-regulated protelomerase expression. This genetic system was recombined into the *E. coli* chromosome to produce conditional recombinase expression strains (R-cells). Also, phage P1 derived Cre telomerase was applied as a positive control, since it's functionality in eukaryotic cells toward generating circular mini-plasmids has been proved. Next, the "supersequence" was designed that carries the multipurpose Cre/Flp/TelN/Tel target sites *loxP-frt-telRL-pal* and flanking 72 bp SV40 enhancer elements to maximize nuclear importation. Supersequence was cloned into two different sites of a eukaryotic vector in order to permits formation of either lcc or ccc eukaryotic mini-plasmid depending on the recombined cell in which it is grown.
Results: were confirmed by digestion and PCR. This temperature-controlled system enables R-cells to produce and recover lcc and ccc mini-plasmids in a one step reaction *in vivo*.
Conclusion: Lcc mini-plasmid vectors have the potential for further development as a novel gene delivery platform without the obstacle of random integration into the host genome and side effects of the bacterial DNA.

106. Effect of the Metabotropic Glutamate Receptor Type 5 Antagonists MPEP and MTEP in Parkinsonian Monkeys

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In the long term approximately 80% of levodopa (L-Dopa) treated patients, the most effective and commonly used treatment for Parkinson disease (PD), will develop abnormal involuntary movements including L-Dopa-induced dyskinesias (LID). Brain glutamate overactivity is well documented in PD and antiglutamatergic drugs have been proposed to relieve PD symptoms and decrease dyskinesias. Metabotropic glutamate receptors are topics of recent interest in PD.
Objective: This study investigated the effects of the metabotropic glutamate receptors type 5 (mGluR5) antagonists MPEP and MTEP on motor behavior in monkeys with a 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) lesion to model PD and treated with L-Dopa the gold standard therapy.
Methods: Six *Macaca fascicularis* MPTP monkeys were initially treated repeatedly with L-Dopa; this treatment increased their locomotion and reduced their parkinsonian scores but induced dyskinesias.
Results: A dose–response of MPEP and MTEP (1.5–30 mg/kg) administered 15 and 30 min respectively prior to L-Dopa, showed that the antiparkinsonian activity of L-Dopa was generally maintained as measured with locomotion and antiparkinsonian scores as well as the onset and duration of the L-Dopa response. Interestingly the

mean dyskinesia score during all the duration of the L-Dopa motor effect, the 1 h peak period dyskinesias scores as well as the maximal dyskinesias scores were dose-dependently reduced with both drugs reaching statistical significance at 10 and 30 mg/kg. A small increase of duration of the L-Dopa effect at 10 and 30 mg/kg of MPEP was measured.

Conclusion: Our results with MPEP and MTEP to reduce LID are comparable with previous findings with amantadine in MPTP monkeys. This study showed a beneficial antidyskinetic effect of blocking mGluR5 in L-Dopa-treated MPTP monkeys thus supporting the therapeutic use of an mGluR5 antagonist to restore normal brain glutamate neurotransmission in PD and decrease dyskinesias. No therapy is yet approved for dyskinesias. mGlu5 receptor antagonist treatment might bring the first therapy for attenuating PD-L-Dopa-induced dyskinesias.

107. Design, Construction and Characterization of Trastuzumab-conjugated Gold Manoparticles (AuNPs) for Enhanced X-radiation Treatment of Locally Advanced Breast Cancer (LABC)

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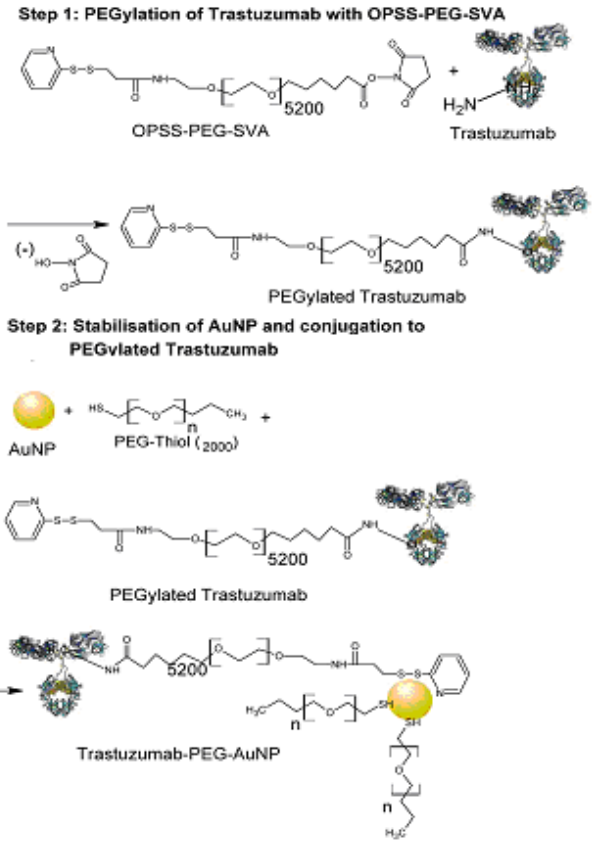
Purpose: Locally advanced breast cancer (LABC) has a poor prognosis despite its anatomical restriction to the breast. Our purpose was to develop a human epidermal growth factor receptor-2 (HER-2) targeted nanotechnology-based radiosensitizer that may enhance the radiation response in LABC and improve the chance for cure. HER-2 is overexpressed in 40-50% of LABC.

Methods: Trastuzumab was derivatized with a polyethylene glycol (PEG) cross-linker to produce trastuzumab-PEG (step 1). These immunoconjugates were analysed by SDS-PAGE and their immunoreactivity assessed by flow cytometry using HER-2 overexpressing SK-BR-3 BC cells. The conjugates were then linked to 30 nm AuNPs (step 2). The specificity for HER-2 dependent internalization was shown by visualizing the uptake of trastuzumab-PEG-AuNPs or PEG-AuNPs by light scattering darkfield microscopy. The ability of trastuzumab-PEG-AuNPs in combination with 100 keV X-rays to enhance potentially lethal DNA double strand breaks (DSBs) in SK-BR-3 cells was assessed by immunofluorescence using the γ-H2AX assay.



Results: Reacting trastuzumab with increasing ratios of PEG caused an increase in the molecular weight (M_r) from ~148 kDa to ~243 kDa, associated with increasing PEG substitution. Flow cytometry revealed 56% retention of immunoreactivity of trastuzumab-PEG relative to trastuzumab. Darkfield imaging showed HER-2 mediated internalization of trastuzumab-PEG-AuNPs in BC cells. Preliminary γ-H2AX assay results revealed 3 fold higher DNA DSBs with traztuzumab-PEG-AuNPs relative to PEG-AuNPs combined with X-irradiation.

Conclusion: Trastuzumab-AuNPs were produced that retained HER-2 immunoreactivity. The enhanced DNA DSBs observed with X-irradiation in BC cells suggests that these AuNPs could potentially improve the response to radiation treatment in LABC.

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108. Protein Arginine *N*-Methyltransferase 1 and 2 Heterodimerization: A New Enzyme?

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Background: Protein arginine *N*-methyltransferases (PRMTs) catalyze post-translational modifications on proteins, contributing to signals that control chromatin organization and cell growth. Some PRMTs act as co-regulators of transcription by methylating arginine residues on histones, transcription factors, and other chromatin-associated proteins. PRMT1 and PRMT2 are both selective for histone H4, but *in vitro* comparisons indicated that PRMT1 is three orders of magnitude more active than PRMT2 despite similar substrate binding. Since dimerization of PRMT1 is essential for its methylation activity, we wanted to investigate possible heterodimerization between PRMT1 and PRMT2. We co-incubated PRMT1 and PRMT2 with the expectation that PRMT2 within the heterodimer complex would lower PRMT1 methylation of histone H4.
Methods: PRMT methylation reactions are qualitatively assessed using gel electrophoresis and phosphor imaging, and PRMT product formation is quantified using an ultra-performance liquid chromatography tandem mass spectrometry assay. The interaction between subunit combinations of PRMT1 and PRMT2 and their sub-cellular localization are demonstrated in HeLa cells using biomolecular fluorescence complementation (BiFC) in which PRMTs are constructed with N- or C-terminal fragments of the fluorescent protein monomeric Citrine, and a functioning fluorescent protein is reconstituted if the PRMTs to which Citrine fragments are attached physically interact.
Results: The addition of PRMT2 to PRMT1 shows a synergistic increase in histone H4 methylation, implying that these two enzymes interact. The observed increase in methylation is attributed to an increase in activity from the PRMT1 subunit as determined using combinations of wildtype and catalytically inactive mutants of PRMT1 and PRMT2. BiFC shows that in addition to homodimers of PRMT1 and PRMT2, heterodimers between PRMT1 and PRMT2 are formed predominantly in the nucleus.
Conclusions: The results of this study demonstrate that PRMT1 and PRMT2 can heterodimerize *in vitro* and in cells, suggesting that PRMT subunits may associate in a combinatorial manner to generate new enzymes with unique functions in controlling cellular processes.

109. Telomerase Inhibition Potentiates the Genotoxic Effects of DNA-Damaging Agents in Breast and Colorectal Cancer Cells

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Background: Telomerase is a specialized reverse transcriptase that maintains telomeres, chromosome end structures that are important to genome stability. Telomerase is over-expressed in more than 90% of human tumors. Normal somatic cells, on the other hand, have low telomerase levels, making the enzyme an appealing target for anticancer therapy. In experimental models of cancer, significant time lags have been observed between the start of telomerase inhibition and the arrest of cancer cell growth. This has dampened expectations for the clinical effectiveness of telomerase inhibition. Aside from its normal role in telomere length regulation, telomerase has also been reported to participate in chromatin maintenance. Genetic suppression of the human telomerase catalytic subunit, telomerase reverse transcriptase (hTERT), diminishes cellular DNA repair following genotoxic damage induction, suggesting that the enzyme is involved in regulating the DNA repair response.
Objective: We hypothesize that transient telomerase inhibition at the time of genotoxic stimulus will increase cytotoxicity in tumor cells. Combination treatments of telomerase inhibitor and the DNA damaging agents are tested in cancer cell models.
Methods: DNA damage was induced in MCF-7 breast cancer cells, and in HT29 and LS180 colorectal cancer cells using different chemotherapeutic agents. Using a well-established clonogenic assay, the genotoxicities of these compounds were determined in the presence and absence of the telomerase inhibitor GRN163L, as well as with the concurrent administration of ATM

inhibitor Ku55933.
Results and Conclusion: We report that short-term telomerase inhibition potentiates the cytotoxic effects of DNA-damaging agents, in a temporal and DNA-damage mechanism-specific manner.

110. Suitability of MDCK Cell Line as a Tool for Intestinal Permeability Screening of Antineoplastic Compounds

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Background: Since most drugs are administered orally, compounds are screened during the drug development process to understand their expected *in vivo* oral absorption characteristics in humans. Among the various available permeability screening tools, CACO-2 (human colon adenocarcinoma cell line) is considered a gold standard. CACO-2 requires 21 days of culture to achieve a polarized monolayer resembling the small intestine, a distinct disadvantage for high throughput screening. MDCK (Madin-Darby Canine Kidney cell line) has a shorter culture period (3 days) and several studies demonstrate a significant correlation between MDCK and CACO-2 permeability results. However, antineoplastic compounds, which have the potential to disrupt monloyer integrity, have not been assessed in MDCK.
Objective: In this study, we evaluated the MDCK cell line as a substitute for CACO-2 for membrane permeability screening of antineoplastic compounds.
Method: We selected a series of antineoplastic compounds synthesized in our laboratory and compared permeability across MDCK and CACO-2 monolayers. CACO-2 and MDCK were grown on Transwell® permeable inserts for 21 days and 3 days, respectively, before 2h incubation with compounds. Transepithelial electrical resistance (TEER) and lucifer yellow (LY) rejection rate was determined to confirm monolayer integrity. Compounds were quantitatively determined by HPLC-UV and apparent permeabilities (P_{app}) were calculated. Based on the P_{app} values, compounds were ranked and a Spearman's rank correlation coefficient was calculated.
Results: MDCK and CACO-2 showed equivalent rank correlation (r_s=1.0) with respect to selected antineoplastic compounds. Coefficient of determinations between apparent permeabilities of compounds (N=6) across MDCK and CACO-2 were 0.72 (apical to basal) and 0.56 (basal to apical) whereas that of efflux ratio was 0.88.
Conclusion: Our data suggest MDCK may substitute for CACO-2 permeability screening of antineoplastic compounds.

111. Mechanism of High Glucose-Induced Activation of the RhoA/Rho-Kinase Pathway in Primary Cardiomyocytes

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Objective: Diabetic cardiomyopathy is a major complication of diabetes and contributes to the increasing incidence of diabetes-related morbidity and mortality. Molecular mechanisms underlying diabetic cardiomyopathy have not been fully elucidated; however, a potential mechanism is the over-activation of the RhoA/Rho-kinase (ROCK) pathway. Separate *in vitro* and *in vivo* studies from our lab have recently found that (1) iNOS is a positive regulator of RhoA expression, and (2) high glucose increases iNOS expression via $PKC\beta_2$ activation in cardiomyocytes. From these findings, we seek to investigate whether high glucose-induced $PKC\beta_2$ activation is associated with over-activity of the RhoA/Rho-kinase pathway. We propose that cardiomyocytes incubated in high glucose exhibit increased RhoA expression and activation of the RhoA/Rho-kinase pathway in a $PKC\beta_2$-dependent mechanism, and these effects are attenuated upon $PKC\beta_2$ inhibition.
Research Methods: Primary ventricular cardiomyocytes were isolated from non-diabetic adult male Wistar rats and allowed to attach on laminin-coated plates for 2-3 hours. Cells were incubated in the following treatments for 24 hours: low glucose; high glucose; mannitol as osmotic control; high glucose in the presence of H-1152, LY-333531 and chelerythrine. Cells were lysed and relative expression of ROCKI, ROCKII and RhoA were determined by immunoblotting. ROCK activity assays were performed by adding an exogenous truncated myosin phosphatase (MYPT1) to cell lysate and the amount of phosphorylated MYPT1 was determined by immunoblotting.
Results and Conclusions: Exposure of cardiomyocytes to high glucose increased RhoA

expression and ROCK activity which was attenuated with PKCβ_2 inhibition. High glucose incubation did not significantly alter ROCKI and ROCKII expression. Surprisingly, ROCK inhibition not only led to decreased ROCK activity but also RhoA expression. PKCβ_2 or ROCK inhibition prevents over-activity of the RhoA/Rho-kinase pathway. These results, combined with a recent study from our lab that ROCK can phosphorylate PKCβ_2 *in vitro*, collectively suggest that PKCβ_2 is an upstream mediator of the RhoA/Rho-kinase pathway and is activated in high glucose possibly through positive feedback mechanism in cardiomyocytes.

112. Förster Resonance Energy Transfer Measurements of Cofactor-Dependent Effects on Protein Arginine *N*-Methyltransferase Homodimerization

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Background: Dimerization of protein arginine *N*-methyltransferases (PRMTs) is required for the transfer of methyl groups from the cofactor *S*-adenosyl-L-methionine (AdoMet) to arginine residues in protein substrates, forming *S*-adenosyl-L-homocysteine (AdoHcy) and methylarginine residues, which help to orchestrate cell-signalling events.
Methods: In this study we use Förster resonance energy transfer (FRET) to determine dissociation constant (K_D) values for homodimerization of PRMT1 and PRMT6. By attaching monomeric Cerulean and Citrine fluorescent proteins to their N-termini, fluorescent PRMTs are formed that exhibit similar enzyme kinetics to unconjugated PRMTs as measured using an ultrahigh performance liquid chromatography tandem mass spectrometry assay to quantify total methylarginine production. These fluorescent proteins are then used in FRET-based binding studies in a multi-well format.
Results: In the presence of AdoMet, fluorescent PRMT1 and PRMT6 exhibit 4- and 6-fold lower dimerization K_D values, respectively, than in the presence of AdoHcy, suggesting that AdoMet promotes PRMT homodimerization in contrast to AdoHcy. We also find that the dimerization K_D values for PRMT1 in the presence of AdoMet or AdoHcy are respectively 6- and 10-fold lower than the corresponding values for PRMT6.
Conclusions: Considering that the affinity of PRMT6 for AdoHcy is 10-fold higher than for AdoMet, PRMT6 function may be subject to cofactor-dependent regulation in cells where the methylation potential (*i.e.*, ratio of AdoMet to AdoHcy) is low. Since PRMT1 affinities for AdoMet and AdoHcy are similar, however, a low methylation potential may not affect PRMT1 function. This work demonstrates how cofactors regulate PRMT activity by controlling subunit dimerization.

113. Effects of HIV Reverse Transcriptase Inhibitors on Human Telomerase

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Background: Accelerated tissue aging is observed in individuals infected with the human immunodeficiency virus (HIV) on long-term highly active antiretroviral therapy (HAART). HAART involves targeting different aspects of HIV biology with selective drug combinations. Two of the most commonly used drug classes in HAART, nucleoside and non-nucleoside reverse transcriptase inhibitors, target HIV reverse transcriptase (RT), a viral enzyme that is essential for HIV infection. Biochemical studies identified mechanistic and structural similarities between HIV RT and telomerase RT, the catalytic subunit of telomerase, an endogenous RT enzyme that maintains telomeres. Telomeres are nucleoprotein complexes that protect chromosome ends and maintain genome stability. Telomere shortening occurs naturally with age. Critically short telomeres prevent further cell division, leading to compromised tissue renewal and the eventual failure of tissue regeneration.
Objective: We hypothesized that HIV RTIs also affect the endogenous activity of telomerase, and that the accelerated aging phenotype observed in HIVpositive individual on long-term HAART could be attributed to telomerase inhibition by HIV RTIs. We tested our hypothesis using an in vitro biochemical assay for telomerase activity, as well as by monitoring telomere length maintenance dynamics in living cells.
Methods: In the first approach, a telomerase activity assay was used to assess both the potency and mechanism of inhibition of each HIV RTI. In the second approach, the effect of long-term HIV RTI

treatment on telomere maintenance was studied in telomerase-positive human cell culture models. Growth characteristics and telomere maintenance dynamics were measured in the presence or absence of single HIV RTIs, as well as in clinically relevant combinations.

Results and Conclusion: We report that Zidovudine (AZT) inhibits telomerase activity in a dose-dependent manner, in agreement with both the data from the in vitro biochemical assay, as well as from the human cell culture approach. Using these assays, the telomerase inhibition potency for each HIV RTI will be measured. We will discuss the clinical relevance of our research findings.

114. Development of A High Performance Liquid Chromatographic Assay for the Simultaneous Determination of Midazolam and Ketoconazole in Rat Plasma and Its Application in a Drug Interaction Study

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Objectives: To develop a high performance liquid chromatographic assay for the simultaneous quantitation of midazolam (MDZ) and ketoconazole (KTZ) in rat plasma, and then to use it in a drug interaction study.

Methods: MDZ, KTZ and diazepam (internal standard) were extracted from 100 µL plasma using diethyl ether in the presence of 0.1N NaOH. After vortexing, centrifugation and freezing, the organic layer was transferred to clean tubes and evaporated. The dried residue was reconstituted in mobile phase and injected into the HPLC through a C18 column. The mobile phase consisted of acetonitrile: 15 mM potassium dihydrogen orthophosphate (45:55, v/v), pumped at 1 mL/min and measured at λ=220 nm. Venous cannulated rats were orally dosed KTZ 40 mg/kg or 1% methylcellulose followed by iv dosing of 5 mg/kg MDZ to rats 1.5 h later, flowed by serial blood sampling.

Results: The components eluted within 10 min; calibration curves were linear ($r^2 \approx 0.999$) over the range of 25-10000 ng/mL of KTZ and MDZ concentrations. The CV and mean error were <20% for both drugs. The validated lower limit of quantitation was 25 ng/mL for both drugs based on 100 µL rat plasma. Rat plasma concentrations of MDZ and KTZ were simultaneously measured up to 8 h and 9.5 h, respectively, yielding the following pharmacokinetic data:

	MDZ (-KTZ)	**MDZ (+KTZ)**	**KTZ (+MDZ)**
$AUC_{0-\infty}$, mg·h/L	2.41±0.60	3.23±0.45*	84.0±25.1
$t_{½}$, h	5.96±4.82	3.13±1.16	0.89±0.33
Clearance, L/h/kg	2.17±0.46	1.57±0.19*	-
Volume of distribution, L/kg	4.46±2.78	3.50±1.03	-
Cmax, mg/L	-	-	23.5±6.4
Tmax, h	-	-	2.67±0.59
*p<0.05 versus MDZ (-KTZ)			

Conclusions: The assay was shown to be rapid, sensitive and appropriate for a pharmacokinetic study. KTZ caused a significant decrease in MDZ clearance.

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115. Intestinal Permeability, Uptake and Metabolism of Flaxseed and Mammalian Lignans in the Caco-2 Cell Monolayer

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Background: Intestinal transcellular permeability, uptake and metabolism across the Caco-2 monolayer are often used for assessing oral drug absorption potential. Upon oral consumption, the major lignan of flaxseed, secoisolariciresinol diglucoside (SDG), undergoes conversion in the upper gastrointestinal tract to secoisolariciresinol (SECO), which is then further metabolised to the mammalian lignans, enterodiol (ED) and enterolactone (EL), by colonic bacteria.

Objective: In this study, we evaluated intestinal permeability, uptake and metabolism of flaxseed lignans (SDG and SECO) and mammalian lignans (ED and EL) using the Caco-2 monolayer.

Method: Caco-2 cells were grown on Transwell® permeable inserts and 24 well tissue culture plates

for 21 days. Lignans were added to Transwell plate assembly at a concentration of 100 μM. Transepithelial Electrical Resistance (TEER) values and Lucifer Yellow rejection was used to assess integrity of the Caco-2 monolayer. For uptake and metabolism studies, lignans were prepared in culture media at a concentration of 100 μM and incubated in Caco-2 cells for 48 hrs. Supernatant and cell pellet were collected at 2, 4, 6, 12, 24 and 48 hours in triplicate. Enzymatic hydrolysis was done and lignans were analysed by HPLC with fluorescence detection.

Results: Apical-to-basal apparent permeability for SECO, ED and EL across Caco-2 were 7.96±0.41, 7.71±0.16 and 13.7±0.20 ($\times 10^{-6}$) cm/s, whereas efflux ratios were 1.19, 1.15 and 0.77, respectively. Concentration of SDG in the acceptor compartment was below limit of quantification; therefore, apparent permeability could not be calculated. After 48 h of incubation, extent of conjugation of SECO, ED and EL was 94.6, 86.9 and >99%, respectively.

Conclusions: SDG has poor permeation characteristic across Caco-2 monolayer system while SECO, ED and EL permeate via passive diffusion. SECO, ED and EL undergo Phase-II conjugation reactions, which may contribute to loss of lignan due to first-pass intestinal metabolism.

Education and Teaching Research

116. A New Analogy for Teaching the Well-stirred Model to Pharmacy Students

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Objective: Educating pharmacy students about the well-stirred model of hepatic drug clearance can be challenging. While students typically grasp the mathematical aspects, they have difficulty with the intuitive and graphical aspects. This study evaluated the effectiveness of using a novel analogy (cartoon consisting of four panels that relate the well-stirred model to patrons in a pub), in addition to a didactic lecture, to improve students' understanding of this model.

Methods: The well-stirred model was the subject of a 2-hour session in an elective pharmacokinetics class consisting of 55 third- and fourth-year students. A 5-point Likert scale questionnaire consisting of seven questions to ascertain students' understanding of the well-stirred model and their confidence in explaining it or applying it in practice was administered twice: pre-test 1 at the beginning of class and pre-test 2 after a 60-minute didactic lecture regarding the mathematics of the model but before a 20-minute PowerPoint presentation of the analogy. At the end of class, students completed a post-test questionnaire containing the same seven questions, plus two additional questions, asking if students felt the analogy helped their understanding more than explanation alone, and if it should be included in next year's class.

Results: There was a significant improvement in students' understanding of the well-stirred model, according to responses to all seven questions between pre-test 1 vs. pre-test 2 vs. post-test ($p<0.05$, *ANOVA with posthoc LSD*), with one exception. Specifically, the analogy led to significant improvement in intuitive and graphical understanding but no additional improvement in mathematical understanding beyond the didactic lecture. Furthermore, 98% of students agreed or strongly agreed that the analogy helped their understanding above explanation alone and should be included next year.

Conclusions: A novel analogy relating the well-stirred model to a social setting of patrons in a pub led to improved student understanding of the model intuitively and graphically and will be incorporated into the course in subsequent years.

117. The Influence of Emotional Intelligence (EI) Training on EI skills in First Year Pharmacy Students at the University of British Columbia

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The magnitude to which prescriptions are not taken as prescribed is a growing social concern. Future pharmacists need the skills and knowledge to communicate with patients and effectively influence their medication-taking behaviours. Studies suggest that if pharmacists establish a trust relationship with the patient, they will be more effective to help resolve preventable drug-therapy problems, such as non-compliance.

Objectives: This randomized controlled study determined whether an emotional intelligence (EI) training program improves pharmacy students' EI scores and performance to perceive and interpret emotional cues during a patient-pharmacist interaction. The study also examined the relationships between EI, student performance, and critical thinking dispositions.
Methods: First year pharmacy students participated in the study by taking the Mayer, Salovey, and Caruso Emotional Intelligence Test (MSCEIT, Mayer, Salovey, & Caruso, 2002) to determine EI. Students were randomly assigned to be in the intervention or control group. In the intervention group, students took the MSCEIT both before and after receiving EI training skills workshop while in the control group, students received the EI workshops after completing both MSCEITs. Finally, all students took the California Critical Thinking Dispositions Inventory (CCTDI, Facione & Facione, 2007) once at the beginning of the study.
Results: EI training significantly improved MSCEIT scores in the intervention group and a weak positive linear relationship between MSCEIT and CCTDI scores was observed.
Conclusions: Implications of the research findings indicate that evidence-based EI training can improve students EI scores. It is evident, however, that students need more exposure to EI training and opportunity to practice EI skills to achieve the level of EI skill mastery necessary to recognize, establish and sustain effective therapeutic relationships.

118. Implementation of a Health Sciences Interfaculty Curriculum on Interprofessional Collaboration at Université de Montréal

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Context: In 2008, faculties of pharmacy, nursing and medicine (including medicine, occupational therapy and nutrition programs) initiated an interprofessional education (IPE) curriculum on collaborative practice.
Objectives: To assess feasibility of interfaculty education activities involving a large cohort of 800 students from 5 different programs.
Methods: First activity objectives were to: 1) introduce collaborative practice concepts; 2) allow exchanges between students; and 3) have students reflect on professional roles. The first activity was divided into 4 blocks: i) e-learning preparatory modules; ii) small group case discussion; iii) testimony of a patient and sibling; and iv) panel of professionnals. Second activity objectives were to: 1) reflect on importance of collaboration in chronic disease management; 2) discover strategies for professional role clarification and negotiation; 3) discover the patient-centered approach; 4) explore concepts of conflict prevention and resolution; 5) produce an intradisciplinary intervention plan (DIP) and an interdisciplinary intervention plan (IIP). The second activity was divided into 3 blocks: i) e-learning preparatory modules; ii) intradisciplinary workshop (DIP preparation); iii) production of an IIP during a simulated interprofessional meeting. Both activities were evaluated by students via on-line forms. Completion of an on-line survey, participation in forums & workshops and written reflective assignments were used to evaluate students.
Results: This project confirmed the feasibility of such activities at our university. Success of the initiative was the result of a combination of dedicated professors and support from department leaders and techno pedagogical team.
Outcomes: In 2009-2010, the social sciences faculty joined the IPE program development initiative. An enhanced version of the first activity was offered to 1096 students from 9 programs (audiology, medicine, nutrition, nursing, occupational therapy, pharmacy, physiotherapy, social work, speech therapy). Deans of the 4 faculties are currently taking steps to further develop these interfaculty activities and formalize them into a recognized 3 credits course.

119. Research to Develop and Evaluate a Professional Development Course for Pharmacists in Women's Health

Nesé Yuksel and Theresa J. Schindel. Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton

Objectives: A key strategic action outlined in the *Blueprint for Pharmacy* is to conduct research to develop and improve education and continuing professional development (CPD) programs.

Addressing the need for education to emphasize foundational skills, we developed and evaluated a multifaceted CPD program on pharmacists' roles in the menopause transition. The objective of the evaluation was to explore the impact of the course on pharmacists' knowledge and confidence and how pharmacists approach patient care in their practice following the course.

Methods: The CPD program consists of a three-day workshop focused on practice skill development including patient assessment, communication, documentation, drug information, and therapeutic decision making. Instructional methods integrated lectures, group discussion, self-directed learning assignments, and simulated patient interactions. The course was evaluated using a mixed methods research design consisting of written surveys immediately before and after the course and semi-structured interviews conducted 9 - 12 months following the course. Approval was received from the University of Alberta Health Research Ethics Board.

Results: Twenty pharmacists attended the course in February 2009. The majority of participants were female, had been practicing for more than 26 years and represented a range of practice settings. There was a significant increase in knowledge scores pre and post course (59% vs. 84%, $p<0.003$). Confidence in patient care skills increased significantly with all aspects of patient care assessed. To date, 14 pharmacists have consented to participate in an interview. While the analysis is still underway, preliminary findings indicate that majority of pharmacists (88%) have implemented patient assessment to varying extents in their practice. Findings of this evaluation have been used to modify and improve the course.

Conclusion: As pharmacy practice shifts towards increasing responsibility for patient care, pharmacy education and CPD programs are evolving to address these needs. This program focussed on foundational skill development and incorporated a variety of active learning strategies. Conducting research on CPD programs facilitates better understanding of the impact on both learning and practice.

120. Development of an Online Pharmacy Clinical Instructor Education Program (CIEP)

Rosemin Kassam, *Mona Kwong*, Angela Kim-Sing. Faculty of Pharmaceutical Sciences, University of British Columbia.

Objectives: (1) To develop an accessible web based preceptor program that provides pharmacy practice educators with the necessary competencies to support experiential learning; (2) To develop preceptor education tools and tips to enhance student delivered patient care at the practice sites; (3) To utilize technology to disseminate the education program in the most cost effective and efficient manner.

Methods: The online CIEP was developed over a 3 year period. The content is based on: (1) results of a needs assessment of over 400 health care preceptors, including pharmacists; (2) focus group discussions; and (3) year end feedback from preceptors. The program was developed using Web Browser and HTML delivery format. It incorporates Flash objects and requires Adobe Reader for PDF content.

Results: The online CIEP consists of three courses: (1) "E-Tips": this includes eight web-based, interactive education modules to help develop the skills and confidence of health care practitioners who educate students in the field. This course was authored by an inter-disciplinary team of health care professionals, and the modules range in topic from setting the stage for clinical teaching to strategies for resolving conflict. (2) An "overview" of the different UBC SPEP courses. (3) "Guide to pharmaceutical care": this includes 13 modules ranging from the philosophy and practice model of pharmaceutical care to suggestions for facilitating pharmaceutical care experiential learning. The online provides tips, interactive activities, and encourages reflection. The modules range between 15 and 60 minutes in length.

Conclusions: A web-based preceptor support program was developed to appeal to those involved in training and supervising pharmacy technicians, other pharmacists, and non-pharmacist personnel. Online CIEP is available at no cost and it allows individuals to explore the program components at their convenience. The challenge is to ensure people use it to help deliver effective learning experiences, and that the modules remain viable and sustainable.

121. Bringing Critical Thinking and Writing Skills to Life

Cheryl A. Sadowski, Marlene Gukert. Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, Alberta, Canada.

Objective: To describe the integration of critical thinking writing assignments into an undergraduate Pediatrics/Geriatrics course.
Methods: Since initiation of the course in 2005, written assignments were incorporated into the Pediatric and Geriatric undergraduate module. The topics related to the unique aspects of aging, psychosocial aspects of care, and ethics and cross-cultural issues that are relevant to these special populations. The format, structure, and number of assignments were modified. The changes made were based on student feedback, student performance, peer review (through the Centre for Writers, U of A), and professor evaluation.
Results: For the first 4 years of the course, the assignments resulted in overall very high marks for the students. However student comments indicated that they were not seeing value in completing the topics assigned. In addition, the professors felt that the assignments were not addressing the primary desired outcome; critical thinking. Following consultation with the Centre for Writers significant changes were made. AFPC outcomes were also included in the assignment outlines so students would see the application of the assignments into the overall curriculum. Specific objects were required for the assignments, including position papers, letters of advocacy, personal reflections, and descriptive analyses. As in previous years students found the assignments challenging, particularly the position papers or reflective analysis. It was also noted by the professors that students had significant difficulty writing to a specific audience. As suggested by the Centre for Writers grading rubrics were developed specific to each assignment and addressed critical thinking, organization and writing technique. Scores in the final year resulted in a much greater distribution in marks.
Conclusion: Most second year pharmacy students demonstrated weak writing skills. Critical thinking was effectively assessed using assignments that were designed in consultation with the Centre for Writers. Students were challenged by diverse topics that were outside of the usual medical topics. Further integration of well structured assignments will be beneficial to encourage and assess critical thinking for pharmacy students.

122. Re-evaluation and Revision of the Neurology Practice Laboratory

Cheryl A. Sadowski, Darren Pasay, Hoan Linh Banh. Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, Alberta, Canada.

Objective: To describe the evaluation and changes made to the third year undergraduate pharmacy practice laboratory in the neurology module.
Methods: The neurology course was chosen as a "test" module for integration of enhanced laboratory exercises. The laboratory was re-evaluated in summer 2009, with delivery of the revised exercises in fall 2009. The laboratory evaluation was qualitative and included feedback from teaching assistants, faculty members, the curriculum committee, and students.
Results: The evaluation process indicated that students had, from 2006-2009, generally enjoyed the laboratory exercises, and had performed extremely well. The faculty members and teaching assistants found the laboratory assignments to be simplistic, noting that the structure did not allow for development or assessment of practice skills. The revisions involved a complete overhaul of the laboratory cases, grading rubric, assessment methods, and teaching assistant training. Key changes included the integration of standardized patients, the implementation of a grading rubric that incorporated communication skills, and the expansion of case studies to include community and hospital/institutional practice. Of the 3 laboratories involving clinical practice cases, the teaching assistants strongly supported the changes, but requested more support and training for assessment. Student performance was highly distributed in terms of marks. For the first time in 4 years, students failed the exercises and were required to complete make-up laboratory assignments. Student evaluation was a bimodal distribution, with most students evaluating the laboratory exercises as very instructive and challenging, while other students were strongly opposed to the changes.
Conclusion: A comprehensive evaluation lead to an improved clinical practice laboratory for the neurology module. The changes were challenging for the faculty to implement, but were greatly supported by the teaching assistants. Many students appreciated the fact that the cases will better prepare them for future examinations and clinical practice.

123. Understanding the Scope of Practice in the Context of Laws and Ethics for Pharmacy Students and Pharmacy Technician Students

Ravina Sanghera, Cheryl Cox, Hoan Linh Banh. University of Alberta, Faculty of Pharmacy and Pharmaceutical Sciences

Objectives: To enhance pharmacy student and pharmacy technician understanding of their collaborative scope of practice in pharmacy.
Methods: During the first year Pharmacy Jurisprudence course for winter 2010, pharmacy and pharmacy technician students participated in a 90 minute seminar to discuss community practice scenarios. The students were divided in 8 small groups of 3 pharmacy students and 1 technician student in each of the six seminars to discuss six scenarios. The scenarios represented common situations that would arise in daily practice, and were designed to highlight roles and role delegation between pharmacists and pharmacy technicians. The format of the exercise was as followS: **Part I** – Individually, students were asked to use their knowledge of the Federal and or provincial legislation and the Alberta College of Pharmacists Code of Ethics to document the role that each would play in a patient care scenario. **Part II** – In small groups, the students discussed the role of two professions in providing care to the patient in the cases. **Part III** – Each group of students presented their responses to pharmacist or pharmacy technician facilitators.
Results: In Part I both pharmacy and technician students were uncertain in identifying the specific roles of each profession in any of the 6 scenarios. However, following the discussions in small groups between the technician and pharmacy students in Part II, the group responses were elaborate and resulted in clearly defined roles for each profession. A key change during the discussions for all groups was that the role of the pharmacy technician expanded significantly.
Conclusions: Group discussion enhanced student expectations of a collaborative role in practice with pharmacy technicians. Group learning had a profound effect and was able to change student perception. Due to the success of this seminar, it is recommended that further collaboration between the two teaching institutions occur to expand the learning of pharmacy students and pharmacy technician students.

124. Pharmacist Initiative: Fetal Alcohol Spectrum Disorder (FASD) Awareness and Prevention Research Project

Sharon Mitchell[1], Karen Mills[2], Tara Hanson[3] on behalf of the Alberta FASD Advisory Committee. [1]Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, [2]Alberta College of Pharmacists (ACP),[3] The Alberta Centre for Child, Family and Community Research, Edmonton, Alberta.

Background: FASD may result in life-long disabilities. Even though it is 100% preventable, ~4,000 babies in Canada are diagnosed each year. Although various health care professionals have been engaged in FASD awareness and prevention efforts, there is little evidence in the literature of Pharmacist involvement in these campaigns.
Objective: This study aimed to determine if Pharmacists, the most accessible health care providers, were interested in participating in FASD awareness and prevention at the community level.
Methods: The Population Research Laboratory, University of Alberta was contracted to conduct a survey focusing on potential roles for pharmacists in the delivery of FASD prevention and awareness messaging to women of childbearing age in Alberta. The survey was developed with input from the Alberta FASD Advisory Committee and the Alberta College of Pharmacists. An on-line survey was distributed to 3,232 community-based, practicing pharmacists across Alberta.
Results: Of the 566 respondents, 62% indicated that they were interested in participating as a community resource in FASD prevention. To play a more active role in FASD prevention, pharmacists felt they could benefit from training about FASD (86.5%), FASD awareness (78.3%), treatment (76.4%), and patient education (74.9%). They also expressed interest in distributing awareness and prevention materials to clients in their communities.
Conclusions: With few exceptions, over half of the Alberta based practicing pharmacists who participated in the study indicated interest in becoming a community resource to prevent FASD. However, participants felt they needed more education in the areas of awareness, treatment and patient education regarding FASD. Our goal is to implement an interdisciplinary education-based knowledge mobilization strategy for pharmacists and pharmacy students based on the results from the *Pharmacist Initiative: FASD Awareness and*

Prevention research project.
Funded by The Ministry of Children and Youth Services, Alberta

Pharmacy Practice Research

125. The Impact of a Multidisciplinary Toxicity Assessment Monitoring Program within an Ambulatory Capecitabine-Radiation Oncology Clinic

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Objectives: 1) To determine the rates of selected endpoints in high risk resectable rectal carcinoma patients receiving oral capecitabine and radiation before the implementation of the multidisciplinary team. 2) To compare these rates to those collected after the implementation of a weekly monitoring program by a multidisciplinary team consisting of pharmacists, nurses and physicians.
Methods: Patients were identified who received oral capecitabine and radiation concurrently in the adjuvant rectal setting. Original prescriptions and radiation information were found on patient charts. Meditech was used to retrieve blood work and visit history. OPIS was useful for finding pertinent patient information, and reviewing notes entered by medical oncologists.
Results: A total of 81 patients were examined in this review, 46 of which constituted the control group and the remaining 35 patients made up the intervention group. Both groups received an average dose of 1500mg. Prior to pharmacist intervention there was an incidence of 23.9% ER visits, and 17.4% of patients were admitted to hospital; upon the implementation of the weekly multidisciplinary capecitabine/radiation clinic these numbers dropped to 11.4% and 8.6% respectively. The implementation of the weekly multidisciplinary capecitabine/radiation clinic increased the frequency of dosing adjustments from 10.9% up to 28.6%. There were more delays in therapy in the intervention group when compared to the controls, a rise from 13% up to 20%. A final endpoint measured was the number of patients who discontinued therapy; the weekly multidisciplinary capcitabine/radiation clinic decreased this rate from 17.4% to 11.4%.
Conclusions: Capecitabine in combination with radiation has the potential to cause many complications that can be diminished with appropriate care and collaboration. The implementation of a weekly multidisciplinary capecitabine/radiation monitoring clinic has been shown to greatly reduce hospital admissions and ER visits for adjuvant rectal cancer patients.
Poster previously presented at the National Oncology Pharmacy Symposium October 23rd to 25th, 2009 held at the Fairmont Château Laurier in Ottawa, Ontario.

126. Oculogyric Crises with Atypical Antipsychotics: A Case Series

Melissa Hawkins[1], David Gardner[1,2], Zenovia Ursuliak[2], Sabina Abidi[2], Michael Teehan[2]. [1]College of Pharmacy, Dalhousie University, [2]Department of Psychiatry, Dalhousie University

Objective/Background: To describe the presentation, course, and treatments of oculogyric crisis (OGC), a rare type of dystonic reaction, caused by atypical antipsychotics in a series of patients with first episode psychosis.
Methods: All patients at the Nova Scotia Early Psychosis Program (NSEPP) with episodes of OGC in the last year while being treated with antipsychotics were identified. Case information was gathered by patient and psychiatrist interviews as well as a comprehensive review of the patients' medical records. Informed consent was provided by all patients.
Results: A review of cases with all clinic physicians identified 5 individuals, representing a 1-year prevalence of 2.1% (5/239). There were 3 men and 2 women, ranging in age from 18 to 24. The most commonly associated antipsychotics were olanzapine and risperidone. Other potentially contributing antipsychotics were quetiapine and loxapine. The most common presenting symptom was sustained and uncontrollable upward eye deviation. The time to onset after initiating antipsychotic treatment varied from 5 months to 2 years with episodes lasting from a few minutes up to 4 hours. OGCs interrupted various activities, including driving, and were extremely distressing. Acute treatment involved benztropine and

benzodiazepines, with mixed results. Patients were switched to other, presumably lower risk treatments including clozapine and quetiapine, with mostly positive results. The problem appears to have been resolved in 3 of 5 patients. In the other 2, symptoms, frequency, and intensity have improved but episodes of OGC continue.

Conclusions: Despite the rarity of OGCs with antipsychotics, we identified a surprisingly high rate of this disturbing, potentially irreversible form of dystonia induced by atypical antipsychotics.

*Presented previously at the Dalhousie College of Pharmacy Research Day, September 17th, 2009, Halifax, NS.

127. The Pharmaceutical Care Clinic

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The Pharmaceutical Care Clinic is a pharmacist-run patient-focused consultation office that is located in the Faculty of Pharmaceutical Sciences building at UBC. At this clinic, pharmacists, who are Faculty members, provide services to patients who would benefit from medication management and informed - shared decision-making regarding their drug therapy. The Assurance System, which is based on Pharmaceutical Care practice, will assist the pharmacists to capture clinical information, and generate letters with recommendations to patients and physicians. The pharmacists will conduct a patient and drug therapy assessments, educate patients regarding the risks and benefits of their present/potential drug therapy in treating their medical conditions, identify and resolve any drug therapy problems, while incorporating the philosophy of shared informed decision-making. The clinic will collaboratively work with all healthcare professionals including, primary care providers, hospital pharmacists and community pharmacists, involved in providing seamless patient-centered care. Patients will come from physician/healthcare provider referral, or self-initiated referral. An initial screening through a web-based informational tool will be used. Initial contact will be via telephone conducted by the pharmacy student/administrator to gather further patient information (lab values, symptoms, medications, allergies, etc). At the scheduled appointment, a pharmacist will verify and review the patient's profile and conduct an assessment to identify any drug therapy problems, identify individualized goals of therapy, develop a care plan, perform an evaluation and schedule a follow-up with the patient. In addition, tools and written information will be provided to aid the patient's in their decision-making for their therapy. Working within the College of Pharmacists' existing regulations, the resolution of the drug therapy problems will involve the use of providing written verbal prescriptions from the primary care provider to be filled at the patient's pharmacy, if needed. The clinic will be used as a training centre for pharmacy students and residents and other inter-professional education opportunities. As the clinic develops, there will be opportunities for follow-up education classes for patients, inter-professional education opportunities and continual delivery of pharmaceutical care.

128. Optimizing the Management of Hemodialysis Catheter Occlusion

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Background: Hemodialysis catheter occlusion compromises hemodialysis adequacy and increases the cost of care. Repeated administration of alteplase to clear occluded catheters typically produces only short-term benefits. A step-by-step algorithm describing when and how to administer alteplase, with an emphasis on earlier catheter replacement in specific cases, may reduce the frequency of alteplase administration. The purpose of this study was to design, implement and evaluate the efficacy of an algorithm to optimize the management of hemodialysis catheter occlusion.

Methods: The study had a prospective quasi-experimental design in two parts. Baseline data on the use of alteplase and catheter exchange were collected during Part I. Part II consisted of algorithm implementation with collection of similar data. Rates of alteplase use and catheter exchange per 1000 catheter days were the primary and secondary outcomes of the study, respectively.

Results: One-hundred and seventy-two catheters in 131 patients were followed up during the course of the study. The majority of the study population were on clopidogrel or aspirin (75%); whereas, 11% were on warfarin. The adjusted rate of alteplase use was

not significantly different after algorithm implementation (Part I vs. Part II relative risk: 1.10; 95% CI: 0.73 – 1.65, p = 0.652). Similarly, catheter exchange rates were not significantly different in both parts of the study (1.12 vs. 1.03 per 1000 catheter-days, p = 0.789). Regression analysis showed that the rate of alteplase use was inversely related to the catheter's age (p = 0.010). In a secondary analysis on a subgroup of patients with occlusion-related catheter exchanges (n = 28), the number of alteplase administrations significantly increased with longer waiting time for catheter exchange (p = 0.019).
Conclusion: The hemodialysis catheter management algorithm was not effective in decreasing the rate of alteplase use. This may be partially explained by greater alteplase use due to longer waiting times for catheter exchange procedures.

129. All-cause Mortality in Elderly Persons Treated with Antipsychotics in Manitoba

Irina Vasilyeva[1], Silvia Alessi-Severini[1], Robert G. Biscontri[2], Colleen J. Metge[1], David M. Collins[1], Murray W. Enns[3]. [1]Faculty of Pharmacy, University of Manitoba, [2]Department of Accounting and Finance, Asper School of Business, University of Manitoba, [3]Department of Psychiatry, Faculty of Medicine, University of Manitoba, Winnipeg, Manitoba, Canada

Objectives: Antipsychotic medications have been widely used in elderly persons to control psychotic symptoms in a variety of diagnoses. Increased prescribing of second-generation agents (SGAs; risperidone, olanzapine and quetiapine) in the past decade has led to significant safety concerns. The aim of our study is to compare all-cause mortality in elderly persons treated with SGAs with that of elderly persons treated with conventional first-generation agents (FGAs; haloperidol, phenothiazines).
Methods: A population-based retrospective cohort study of all adults aged 65 and over in Manitoba, who were dispensed antipsychotic medications for the first time (incident users) during the period from April 1, 2000 to March 31, 2007, has been conducted using Manitoba Health administrative databases housed at the Manitoba Centre for Health Policy.
Results: After controlling for potential confounders (e.g., demographics, comorbidity and medication use), there was no significant difference between FGA- and SGA-users in all-cause mortality (adjusted HR 0.890, 95% CI: 0.778 to 1.018).
Conclusions: Preliminary analyses did not show a significantly different risk of all-cause mortality between FGA- and SGA-treated persons. Further analyses will contrast all-cause mortality in elderly individuals treated with antipsychotic agents, compared to matched individuals who had not received antipsychotic medications.
Acknowledgments: This project has been funded by the Manitoba Medical Service Foundation (MMSF). Irina Vasilyeva is supported by the Manitoba Health Research Council (MHRC) Graduate Studentship Award.

130. Systematic Review of Osteoporosis Interventions in Pharmacy Practice

Mary N. Elias, Andrea M. Burden, Suzanne M. Cadarette. Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, ON Canada

Objective: Complete a systematic review of the literature to examine the impact of pharmacist interventions in narrowing the two main gaps in osteoporosis management: identifying at-risk individuals, and improving adherence to therapy.
Methods: We searched the electronic databases of EMBASE, HealthStar, *International Pharmaceutical Abstracts*, and MEDLINE from inception to December 2009, examined grey literature and completed manual searches to identify English-language research that examined osteoporosis management interventions in pharmacy practice. We did not exclude studies based on quality, yet focus on the evidence of effects from controlled studies.
Results: We identified 21 eligible studies: 3 cross-sectional, 1 historical/ecological control, 14 cohort (3 controlled), and 3 randomized controlled trials. Interventions varied from simple educational programs for patients and/or health care professionals, to patient-file review and consultation, to screening based on risk factors or bone mineral density testing and subsequent physician referrals or contact. Results suggest that pharmacy interventions can increase patient awareness of osteoporosis, improve calcium and vitamin D supplementation, identify high risk patients and improve pharmacoprevention. No study examined the impact of pharmacist intervention on treatment adherence or fracture reduction.
Conclusions: Few high-quality studies have examined osteoporosis interventions within

pharmacy practice. Data support potential benefits, such as increased patient awareness and calcium/vitamin D supplementation, as well as improved identification of high-risk patients and subsequent treatment. Pharmacists are well positioned to reduce the burden of osteoporosis by identifying at-risk individuals and improving patient adherence to therapy. More high-quality research/evidence is needed to determine the comparative effectiveness of different pharmacy intervention strategies.

Acknowledgments: Ms. Elias is supported by a Canadian Institutes of Health Research (CIHR) Fredrick Banting and Charles Best Scholarship Master's Award and Dr. Cadarette is supported by a CIHR New Investigator Award in the Area of Aging and Osteoporosis. This work has been accepted for oral presentation at the *Canadian Pharmacists Association Annual National Conference,* May 16th 2010, Calgary, AB Canada.

131. Drug-Induced Hepatic Cholestasis in the ICU: A Case Control Study

David Williamson[1], *Marie-Eve Bédard Dufresne*[2]; Valérie Bonhomme[3]; Martin Albert[1]; Colin Verdant[1]; Anne Julie Frenette[1]. [1]HSCM, Montreal Canada; [2]CH Honore-Mercier, St-Hyacinthe Canada; [3]HMR, Montreal Canada

Introduction: Liver dysfunction in critically ill patients represents a major concern. Many drugs used in the intensive care unit (ICU) have been associated with hepatotoxicity. Hepatotoxicity presents in three distinct patterns: cholestatic, hepatocellular and mixed. No published studies have assessed the drug-induced cholestastic pattern of hepatotoxicity in the ICU.

Objectives: To assess whether use of pharmacological classes previously associated with cholestasis are associated with an increased risk of pure or mixed cholestasis in the ICU.

Methods: A nested case-control study assessed the potential association between use of specified pharmacological classes and cholestasis. Cases were identified from a cohort of patients admitted ≥ 24 hours in whom at least one value of AP < 240 IU/L had been obtained in the 72 hours following admission. We excluded patients with an identified cause of cholestasis as well as patients with bone metastasis and pregnant women. Each case subject was matched to a control subject based on age, gender, and length of ICU stay and admission year. Exposure to antiepileptics, penicillins, cephalosporins, carbapenems, macrolid antibiotics and parenteral nutrition was collected and included in a multivariate conditional logistic regression analysis with known risk factors.

Results: A total of 113 patients developed cholestasis between May 2001 and March 2009 of which 95 had no identified cause. We matched 95 cases with 95 controls and controlled for APACHE II score, sepsis, obesity, diabetes, length of stay and prior history of cholestasis. In multivariate logistic regression, parenteral nutrition (OR 6.26), sepsis (OR 4.05), and penicillins (OR 3.97) were independently associated with cholestasis.

Conclusions: Cholestasis in the ICU often remains of unknown origin. In our study, sepsis, parenteral nutrition and penicillins were independently associated with the development of cholestasis in patients admitted to the ICU.

Also presented to the 30th ISICEM (9/3/2010 - 12/3/2010)

University Posters

132. University Laval

133. University of British Columbia

134. University of British Columbia

135. University of Saskatchewan

136. University of Waterloo

Registrants

(as of May 19, 2010)

Abdelhamid, Ghada	University of Alberta
Aboutabl, Mona	University of Alberta
Aeng, Elissa	University of British Columbia
Allen, Christine	Faculty of Pharmacy, University of Toronto
Allen, Theresa	University of Alberta
Alsaad, Abdulaziz	University of Alberta
Alshamsan, Aws	University of Alberta
Althurwi, Hassan	University of Alberta
Amara, Issa	University of Alberta
Amiji, Mansoor	Northeastern University, Boston
Bacanek, Dara	Biovail Contract Research
Badea, Ildiko	University of Saskatchewan
Bains, Onkar	University of British Columbia
Bally, Marcel	BC Cancer Agency
Bandy, Laura	University of British Columbia
Barralet, Jake	McGill University
Bendayan, Reina	University of Toronto
Bertram, Rebecca	Washington State University
Bhandari, Krishna	University of Alberta
Bhathena, Anahita	Abbott
Binkhathlan, Ziyad	University of Alberta
Blume, Henning	Bayer Inc.
Boivin, Taryn	Cardiome Pharma Corp.
Brocks, Dion	University of Alberta
Brunck, Lynne	Bayer Inc.
Burczynski, Frank	Faculty of Pharmacy, University of Manitoba
Burt, Helen	University of British Columbia
Chakraborti, Michelle	University of British Columbia
Chan, Ken	Xenon Pharmaceuticals Inc.
Chang, Thomas	University of British Columbia
Chhatre, Vinay	Northern Lipids Inc.
Choudhri, Shurjeel	Bayer Inc.
Cosic, Marija	Xenon Pharmaceuticals Inc.
Crawford, Jason	Centre for Drug Research and Development
Cullis, Pieter	Centre for Drug Research and Development
Cummins, Carolyn	Faculty of Pharmacy, University of Toronto
Dadashzadeh, Simin	Shaheed Beheshti University of Medical Sciences
Davies, Neal	Washington State University
Devarajan, Sanj	ratiopharm Inc.
Doschak, Michael	University of Alberta
El Gendy, Mohamed	University of Alberta
El Sayed, Dalia	Faculty of Pharmacy, University of Alberta
El-Bagory, Ibrahim	King Saud University
El-Kadi, Ayman	University of Alberta
Elsherbiny, Marwa	Faculty of Pharmacy, University of Alberta
El-Sikhry, Haitham	University of Alberta
Eastman, Simon	Northern Lipids Inc.

Endrenyi, Laszlo	University of Toronto
Eweka, Prince	North West University
Faan, Clara	BRI Biopharmaceutical Research Inc.
Fediuk, Daryl	University of Manitoba
Ferdinand, Mark	Rx&D
Forster, Joanne	Gattefosse Canada Inc.
Foster, Brian	Health Canada
Fraser, Robert	Centre for Drug Research and Development
Gershkovich, Pavel	University of British Columbia
Ghaffari, Solmaz	Isfahan University Of Medical Sciences
Gilchrist, Sam	University of British Columbia
Gill, Amrit	FMC BioPolymer
Gong, Yuewen	University of Manitoba
Grainger, David	University of Utah
Hamodat, Sarai	Memorial University of Newfoundland
Harasym, Troy	Celator Pharmaceuticals
Hope, Michael	AlCana Technologies
Huang, Leaf	University of North Carolina - Chapel Hill
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Index

F

G

H

I

J

K

L

M

N

O

P

Q

R

Z