

**CSPS 7th Annual Symposium**

**Molecule to market: biotechnologically-derived  
molecules vs traditional small chemical entities.**

June 9-12 2004

The Sheraton Vancouver Wall Centre  
1088 Burrard Street  
**Vancouver**  
**British Columbia**  
**Canada**



**Scientific Planning Committee Chairs**

Gordon McKay, Ph.D., Pharmalytics Inc., Saskatchewan

Dion Brocks, Ph.D., University of Alberta, Alberta

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Effect of a lipoidic excipient on the absorption profile of compound UK81252 in dogs after oral administration.

Biliary excretion of irinotecan and its metabolites.

Definition of a novel atomic index for QSAR: the refractotopological state.

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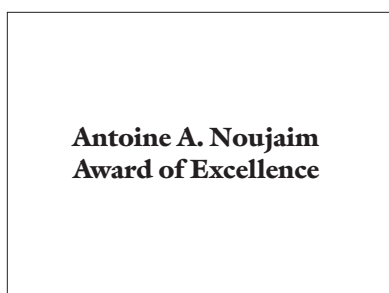
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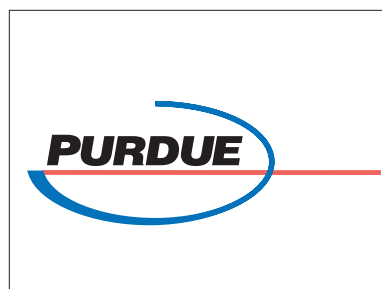
### Gold



### Silver



### Bronze



## 7th Symposium programme - Molecule to market: biotechnologically-derived molecules vs traditional small chemical entities.

Wednesday, June 9, 2004

6:00 pm-7:00 pm. *Registration*, Foyer, Grand Ballroom Level

6:00 pm-8:00 pm. *Wine & Cheese Reception*, Grand Ballrooms C&D

Thursday, June 10, 2004

8:00 a.m.-5:00 p.m. *CSPS Poster Presentations*, Grand Ballrooms C&D. Chairs: Aryn Sayani, GlaxoSmithKline, Mississauga, Ontario, Canada; Lakshmi Kotra, University of Toronto, Ontario, Canada

8:30 a.m.-5:00 p.m. *Symposium*, Grand Ballroom A

8:30 a.m. *Welcome*, Programme Chairs: Gordon McKay, PharmaLytics Inc., Saskatoon, Saskatchewan, Canada; Dion Brocks, University of Alberta, Edmonton, Alberta, Canada

8:35 a.m. *Presentation of Merck Company Foundation Undergraduate Summer Studentship Programme Research Award Recipients* by Kishor Wasan, University of British Columbia, Vancouver, Canada

**Session 1:** *New challenges to drug discovery: small synthetic and biotech-derived chemical entities.* Chair: John H. McNeill, University of British Columbia, Vancouver, BC, Canada

8:45 a.m. **Lorne Babiuk**, Director, Vaccine & Infectious Disease Organization, University of Saskatchewan, Saskatoon, Saskatchewan, Canada. *Novel vaccine formulations & delivery methods.*

9:25 a.m. **Chris Orvig**, Professor, Department of Chemistry, University of British Columbia, Vancouver, British Columbia, Canada. *Medicinal Inorganic Chemistry: Insulin-Enhancing Vanadium Compounds.*

10:05 a.m. **Coffee/Tea Break.** Meet the CSPS poster presenters.

10:35 a.m. **Gary J. Bridger**, Vice-President, Research and Development & Chief Scientific Officer, AnorMED Inc., Langley, British Columbia, Canada. *Small Molecule Chemokine Receptor Antagonists.*

11:15 a.m. **J. Kevin Judice**, Senior Director, Medicinal Chemistry, Genentech Inc, South San Francisco, California, USA. *Proteins vs smallmolecules: lessons from Avastin & Gleevec.*

Noon **Lunch Break.** Meet the CSPS poster presenters.

**Session 2:** *Special considerations in formulating new chemical entities derived from biotechnology.* Chairs: Pieter Cullis, Inex Pharmaceuticals Corporation, Burnaby, British Columbia, Canada; Theresa M. Allen, University of Alberta, Edmonton, Alberta, Canada. **Cosponsored by the International Liposome Society.**

2:00 p.m. **Ian MacLachlan**, Chief Scientific Officer, Protiva Biotherapeutics, Burnaby, British Columbia, Canada. *Considerations for the Development of Nucleic Acid Based Drugs.*

2:40 p.m. **Christine J. Allen**, Assistant Professor, Pharmaceutical Sciences, Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, Ontario, Canada. *Design of Novel Biocompatible, Biodegradable Materials from Consideration of Polymer-Drug Miscibility.*

3:20 p.m. **Coffee/Tea Break.** Meet the CSPS poster presenters.

3:40 p.m. **Michael J. Hope**, Principal Scientist, Inex Pharmaceuticals Corporation, Burnaby, British Columbia, Canada. *Formulation and delivery of oligonucleotides for immunotherapy.*

4:20 p.m. **Theresa M. Allen**, Professor, Department of Pharmacology, and Adjunct Professor, Department of Oncology, Faculty of Medicine & Dentistry, University of Alberta, Edmonton, Alberta, Canada. *Antibody-mediated targeting of antiproliferative antisense oligonucleotides in vitro and in vivo.*

5:00 p.m. *CSPS Members Annual General Meeting, Grand Ballroom A*

Friday, June 11, 2004

8:00 a.m.-5:00 p.m. *AFPC Poster Presentations*, Grand Ballrooms C&D

8:30 a.m.-5:00 p.m. *Symposium*, Grand Ballroom A

**Session 3:** *Analytical issues related to synthetic and biotech-derived molecules.* Chairs: Gordon McKay, PharmaLytics Inc., Saskatoon, Saskatchewan, Canada; Yiu-Chung Lee, Patheon YM Inc., Mississauga, Ontario, Canada. **Cosponsored by the Calibration Validation Group.**

8:30 a.m. *Opening Remarks.* Chairs: Gordon McKay, Yiu-Chung Lee

8:45 a.m. **Fabio Garofolo**, Bioanalysis & PK Head, Vicuron Pharmaceuticals Inc., Gerenzano, Italy. *Quantitative Analysis of Bio-Technologically Derived Pharmaceutical Product by LC-MS/MS.*

9:25 a.m. **Alexander W. Bell**, Team Leader/Professional Associate, Data Interpretation Unit, Montreal Proteomics Network, McGill University, Montreal, Quebec, Canada. *Proteomics analysis of the detoxification machinery in rat hepatic endoplasmic reticulum.*

10:05 a.m. **Coffee/Tea Break.** Meet the AFPC poster presenters.

10:35 a.m. **Bori Shushan**, Manager, Business Development, MDS Sciex, Concord, Ontario, Canada. *Novel hybrid mass spectrometer systems for pharmaceutical research and development.*

11:15 a.m. **Russell S. Weiner**, Associate Director, Clinical Discovery-Immunology, Bristol-Myers Squibb Company, Princeton, New Jersey, USA. *Consensus guidelines for the development and validation of immunochemistry assays for pharmacokinetic studies of macromolecules.*

Noon **Lunch Break.** Meet the AFPC poster presenters.

**Session 4: *Special topics in pharmacokinetics and drug metabolism: small synthetic and biotech-derived entities.*** Chairs: Micheline Piquette-Miller, University of Toronto, Toronto, Ontario, Canada; Dion Brocks, University of Alberta, Edmonton, Alberta, Canada

2:00 p.m. **Charles B. Davis**, Director, Preclinical Drug Discovery, Microbial, Musculoskeletal and Proliferative Diseases, Center of Excellence for Drug Discovery, GlaxoSmithKline Research & Development, Collegeville, Pennsylvania, USA. *Impact of the Pharmacologic Target on the Disposition of Therapeutic Proteins.*

2:40 p.m. **Reza Mehvar**, Professor, School of Pharmacy, Texas Tech University Health Sciences Center, Amarillo, Texas, USA. *Pharmacokinetics and Pharmacodynamics of Polysaccharide-Based Macromolecular Prodrugs.*

3:20 p.m. **Coffee/Tea Break.** Meet the AFPC poster presenters.

3:40 p.m. **Micheline Piquette-Miller**, Associate Professor, Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, Ontario, Canada. *Role of carrier-mediated transport systems in the optimization of drug delivery and response.*

4:20 p.m. **Raymond M. Reilly**, Scientist, Toronto General Research Institute, University Health Network and Associate Professor, Leslie Dan Faculty of Pharmacy and Department of Medical Imaging, University of Toronto, Ontario, Canada. *Visualizing the pharmacokinetics and tissue distribution of novel biopharmaceuticals by molecular imaging techniques.*

6:00 p.m. **CSPS Dinner & Awards**, Grand Ballroom A

## Saturday, June 12, 2004

8:30 a.m.-Noon. *Symposium*, Grand Ballroom A

**Session 5: *Regulatory issues faced in development of small synthetic and biotech-derived entities.*** Chairs: Brian Foster, Health Canada, Ottawa, Ontario, Canada; Pollen Yeung, Dalhousie University, Halifax, Nova Scotia, Canada

8:30 a.m. *Opening Remarks.* Chairs: Brian Foster, Pollen Yeung

8:45 a.m. **David Kwok**, President & CEO, BRI Biopharmaceutical Research Inc., Vancouver, British Columbia, Canada. *The path & strategies for the development of synthetic small molecules & biotechnology-derived new drug candidate.*

9:25 a.m. **Brian Foster**, Therapeutic Products Directorate, Health Canada, Ottawa, Ontario, Canada. *Emerging Regulatory Issues: The Health Canada Perspective.*

10:05 a.m. **Coffee/Tea Break.**

**Session 6: *Roundtable discussion: pharmaceutical scientists and society: is the supply meeting the demand?*** Chairs: Frank Abbott, Vancouver, British Columbia, Canada; Fakhreddin Jamali, Edmonton, Alberta, Canada

10:35 a.m. Joint Session with AFPC

11:55 a.m. **Closing:** Gordon McKay, President, CSPS

**Exhibits**, Wednesday, June 9, 6 p.m.-8 p.m.; Thursday & Friday, June 10 & 11, 9:00 a.m.-4:00 p.m., Grand Ballrooms C&D, North Tower, Sheraton Vancouver Wall Centre

**Symposia**, Thursday, Friday, 8:00 a.m.-5:00 p.m.; Saturday, 8:00 a.m.-noon, Grand Ballroom A, North Tower, Sheraton Vancouver Wall Centre

**CSPS Council Meeting**, Thursday, June 10, 7:00 a.m.-8:00 a.m., Gulf Islands Room A, North Tower, Sheraton Vancouver Wall Centre

**CSPS Annual Meeting**, Thursday, June 10, 5:00 p.m.-6:00 p.m., Grand Ballroom A, North Tower, Sheraton Vancouver Wall Centre

**CSPS Dinner & Awards**, Friday, June 11, 6:00 p.m.-9:00 p.m., Grand Ballroom A, North Tower, Sheraton Vancouver Wall Centre

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**Gordon McKay**

*CSPS President,  
Chair of the Scientific Meeting*

Dr. Gordon McKay received his BSc and Ph.D. degrees in biochemistry from the University of Saskatchewan. After a brief postdoctoral training period in pharmaceutical science, he was appointed as a research associate and adjunct professor of pharmacy in the College of Pharmacy at the University of Saskatchewan and a principal investigator in the Drug Metabolism, Drug Disposition Research Group headed by Dr. Kamal K. Midha at this same institution. The research group received the first program grant awarded by the Medical Research Council to a College of Pharmacy and the first ever awarded to the University of Saskatchewan. This research was renewed for a total of 11 years after which the group began to focus on collaborative research with the pharmaceutical industry and has continued in this regard for almost 25 years. Dr. McKay was awarded fellowship in the American Association of Pharmaceutical Sciences in 1994 for his original contributions to pharmaceutical analysis and was one of the founding members of the Canadian Society of Pharmaceutical Sciences on whose executive he is now the President. He is a scientific organizer for numerous scientific meetings including the Bioanalytical Validation meetings, the Tandem Mass Spectrometry Workshops held annually for the last 15 years and BioInternational. He has served on the editorial board for J.Pharm.Sci. and has been a member of the Pharmaceutical Sciences review committee for MRC and has served on numerous University Boards and Committees. Dr. McKay has published more than 165 original scientific publications and authored more than 200 scientific presentations. Currently he is the chief executive officer for a new not for profit research institute at the University of Saskatchewan which is focused on collaborative research with the pharmaceutical industry aimed at discovering, developing and training in the areas of pharmaceutical science.

**Dion Brocks**

*CSPS Member-At-Large,  
Chair of the Scientific Meeting*

Dr. Dion Brocks, who was elected Member at Large of CSPS in 2003, received is holder of BSc., B.Sc.(Pharm), M.Pharm. (Clinical pharmacy), and PhD. degrees, all received from the University of Alberta. Prior to commencing his academic career, Dr. Brocks worked as in hospital and community pharmacies in Alberta, and after receipt of his M.Pharm. degree, as Clinical Coordinator at the Rockyview Hospital Pharmacy department in Calgary. He received his doctoral degree in Pharmaceutical Sciences, specializing in Pharmacokinetics, in 1993. Dr. Brocks 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 suburban Los Angeles as Associate Professor of Pharmaceutical Sciences. He taught pharmacokinetics and pursued his research interests there until January 2002, when he returned to his alma mater as Associate Professor of Pharmaceutical Sciences. Dr. Brocks has published over 45 peer-reviewed manuscripts related to pharmacokinetics, and has numerous published abstracts and some book chapters. He has served as a member of the editorial board of the Journal of Clinical Pharmacology since 1996, has served as a peer reviewer for a number of journals in the pharmaceutical sciences. His current research interests lie in the study of stereoselectivity, and the effects of lipoproteins, on the pharmacokinetics of drugs. Dr. Brocks' research endeavours are currently funded by a grant from the Canadian Institutes of Health Research.

**Merck Company Foundation Undergraduate  
Summer Student Award Recipients and  
Poster Competition**

Kishor M. Wasan, National Director, Faculty of  
Pharmaceutical Sciences, University of B.C.

In order to encourage pharmacy students to go into research, funding in the form of research fellowships was established to give students an opportunity to work over the summer in research laboratories in all AFPC accredited Pharmacy Schools across Canada. The criteria of selection was based on academic excellence (i.e. grades), letters of reference and evidence of service to the faculty. Selection of the winners was determined by March 1<sup>st</sup> and all the winners and supervisors' names and a summary of their research project were sent to Merck Company Foundation.

## SESSION 1

New challenges to drug discovery:  
small synthetic and biotech-derived chemical entities.



**John McNeill**

Professor and Dean Emeritus, Faculty of  
Pharmaceutical Sciences, University of British  
Columbia, Vancouver, British Columbia, Canada

Dr. John McNeill received his BSc (Pharm) and MSc from the Faculty of Pharmacy University of Alberta in 1960 and 1962. He taught at the College of Pharmacy, Dalhousie University for one year before entering the PhD program at the Department of Pharmacology University of Michigan where he completed his degree in 1967. He taught pharmacology at the College of Medicine, Michigan State University before returning to Canada in 1971 to the Faculty of Pharmaceutical Sciences at UBC. Subsequently he achieved Full Professorship and served as Associate Dean for 6 years followed by nearly 12 years as Dean. Dr. McNeill has maintained his research program throughout his career. His early work was concerned with metabolic processes in the heart and he became interested in cardiac changes in diabetes. His lab was one of the first to investigate the mechanisms underlying diabetic cardiomyopathy and his observation that vanadate treatment prevented the onset of the diabetic cardiomyopathy set the stage for his subsequent research on vanadium as a treatment for diabetes. His latest interest is in the role of insulin resistance in experimental hypertension. In addition, he is the principal investigator on a program grant that is examining the role of lipotoxicity in the cardiovascular complications of diabetes. A major focus in Dr. McNeill's career has been the training of graduate students and postdoctoral fellows. He has trained more than 20 postdoctoral fellows, more than forty graduate students, and has had 10 visiting professors spend time in his lab. These individuals have gone on to excellent careers of their own in Canada, the United States, the United Kingdom, France and Japan. His work, more than 900 manuscripts, abstracts and review articles, has been cited more than 6200 times. He was elected to the Royal Society of Canada and the International Academy of Cardiovascular Sciences. He has been continuously funded by MRC/CIHR and the Heart and Stroke Foundation since 1972. Dr. McNeill has served on and chaired grant committees for MRC, Heart and Stroke Foundation of Canada, Canadian Diabetes Association and the Rx&D Health Research Foundation and on numerous editorial boards. He was President of the Pharmacological Society of Canada, the Western Pharmacology Society, the Association of Deans of Pharmacy, the Canadian Council on Animal Care and the Canadian Foundation for Pharmacy. He is also an outstanding teacher, having won the Killam Teaching Prize at UBC.

## Novel Vaccine Formulations and Delivery Methods

Lorne A. Babiuk, Vaccine and Infectious Disease Organization, University of Saskatchewan, Saskatoon, Saskatchewan, Canada

Recent advances in genomics, molecular biology, and immunology have increased the speed with which protective antigens from many pathogens can be identified. A description of methods to identify antigens will be described. Furthermore, advances in antigen production methodology have made these antigens available in large quantities for use in vaccine protocols. Unfortunately, no matter how good an antigen one has, if they are not formulated or delivered properly, their full value will not be achieved. Since alum, the adjuvant employed in the majority of vaccines today, skews the immune response to a Th2-like immune response, the search continues for better adjuvants to give a balanced immune response. The recent discovery that CpG motifs can act as danger signals has led to their investigation as possible stimulators of innate and specific immunity. In order to identify optimal sequences for stimulating immune cells *in vitro*, we initially screened a large number of different CpG motifs in a lymphocyte proliferation assay and identified motifs that could stimulate lymphocytes *in vitro*. Using these stimulatory motifs, we tested their ability to serve as therapeutics to prevent infection and as adjuvants to enhance immune responses *in vivo*. Interestingly, these motifs could not only act as adjuvants when mixed with antigens, but could shift the response to a more balanced one if they were administered with peptides, subunit antigens, or conventional vaccines. In addition to its potential to enhance immune responses and act as an immune modulator, these motifs induced much less tissue reaction than do other conventional adjuvants. A second adjuvant based on polyphosphazenes also dramatically enhanced immune responses to vaccines and provided a more balanced response. Finally, combining CpG with polyphosphazenes further enhanced the magnitude of the response. The use of these novel adjuvants in enhancing vaccine efficacy and providing opportunities for novel delivery modalities will be described. [babiuk@sask.usask.ca](mailto:babiuk@sask.usask.ca)

## Lorne Babiuk

Director, Vaccine and Infectious Disease Organization, University of Saskatchewan, Saskatoon, Saskatchewan, Canada

Dr. Babiuk is the Director of the Vaccine & Infectious Disease Organization (VIDO) and Canada Research Chair in Vaccinology in Saskatoon, Saskatchewan. Under his direction, VIDO has become internationally recognized for its role in the use of biotechnology to develop vaccines. The world's first genetically engineered vaccine for animal species was developed at VIDO. He has held prestigious national and international awards for excellence in research and for transferring research into the commercial arena including an NSERC Chair in Biotechnology, Canadian Society of Microbiology Award, Xerox-Canada Forum Award; served as a member of the Scientific Advisory Board or Board of Directors for numerous companies involved in commercializing biological research and as a consultant to Genetech, Molecular Genetics Inc., CIBA-GIEGY; conducted due diligence studies for investors and companies regarding the commercial potential of specific scientific proposals. He has mentored over 90 graduate students and post-doctoral fellows who have obtained positions in industry, academia and government, served as a member of many grant and government committees and a reviewer for various scientific journals, as well as serving on general editorial boards. He has published over 400 peer-reviewed manuscripts and 80 book chapters and reviews, and is holder of 20 issued patents and 18 patents pending. His special areas of research are in molecular virology, vaccinology, immunology, and viral pathogenesis with emphasis on respiratory and viral infections. Recent interest has been in novel vaccine development using genomics and in delivery to induce mucosal immunity, as well as helping set science policy in Canada. In addition to being a visionary, he is also an accomplished fundraiser and builder of people and facilities by the recent completion of a \$19 million research wing and the current construction of a \$62 million level III biocontainment facility.

## Medicinal Inorganic Chemistry: Insulin-Enhancing Vanadium Compounds

Chris Orvig, Department of Chemistry, University of British Columbia, Vancouver, British Columbia, Canada

Many metallic elements play crucial roles in living systems - natural evolution has incorporated metal ions into essential biological functions such as oxygen transport, oxidation and reduction, and photosynthesis. Metal ions such as zinc provide the structural framework for the zinc fingers that regulate the function of genes in the nuclei of cells, and calcium-containing minerals are the basis of bones, teeth and shells. Zinc is also a natural component of insulin, and metals such as copper, zinc, iron and manganese are incorporated into catalytic metalloenzymes. One third of all enzymes known are metalloenzymes. With all of these natural functions enabled by metal ions, it is natural to speculate that metals ought to have a role in pharmaceutical applications as well. Medicinal inorganic chemistry as a discipline has only existed for the last 30 years or so, since the discovery of the antitumour activity of cisplatin,  $\text{cis-}[\text{Pt}(\text{NH}_3)_2\text{Cl}_2]$ ; however, it has been practiced, however, for almost 5,000 years. As far back as 3,000 B.C., the Egyptians used copper to sterilize water, and gold was used in a variety of medicines in Arabia and China 3,500 years ago. The first structure-activity relationship (SAR) was realized by Paul Ehrlich, in the first decade of the 20<sup>th</sup> century, with the inorganic compound arsphenamine (otherwise known as Salvarsan or Ehrlich 606) as a successful treatment for syphilis. In this lecture, we will discuss aspects of medicinal inorganic chemistry, with examples from our own research, specifically from our development (with Dr. J. H. McNeill) of insulin-enhancing vanadium compounds as pharmaceuticals for the management of diabetes mellitus. The preparations, reaction chemistry and structures of several of these compounds will be presented, along with pertinent spectroscopic, pharmacological and 48V biodistribution data, as well as a model for the uptake and distribution of vanadium.

## Chris Orvig

Professor of Chemistry and Pharmaceutical Sciences, Department of Chemistry, University of British Columbia, Vancouver, British Columbia, Canada

Chris Orvig was born and raised in Montréal. He received his B.Sc. in chemistry from McGill University in 1976 and subsequently pursued graduate studies (as a Natural Sciences and Engineering Research Council - NSERC - of Canada scholar) in technetium chemistry at M.I.T. with Prof. Alan Davison, receiving the Ph.D. in 1981. He was then an NSERC postdoctoral fellow with Prof. Kenneth N. Raymond at the University of California, Berkeley in 1981-83. After one year with the late Prof. Colin J. L. Lock at McMaster University, he joined the faculty of the Department of Chemistry at the University of British Columbia in 1984, where he is now Professor of Chemistry and Pharmaceutical Sciences, and Director of the Medicinal Inorganic Chemistry Group, as well as graduate advisor. His scientific interests are firmly planted in the areas of medicinal inorganic chemistry and coordination chemistry - he has been involved over the years with radiopharmaceutical chemistry, metal ion decorporation, metal ion neurotoxicology, and chemotherapeutic metal complexes. Orvig is the inorganic chemistry editor of *Can. J. Chem.* and sits on numerous editorial boards and advisory panels. He has received various research and teaching awards, has published more than 130 research papers, and is a co-inventor on many issued patents (including ten from the USA).

**Small molecule chemokine receptor antagonists.**

**Gary J. Bridger**, AnorMED Inc., Langley, British Columbia, Canada

CD34+ hematopoietic progenitor cells are currently collected for clinical transplantation purposes following mobilization to the peripheral blood by administration of granulocyte colony stimulating factor (G-CSF) to donors. The chemokine stromal cell-derived factor 1 (SDF-1) and its cognate receptor, CXCR4, are recognized to play key regulatory roles in the trafficking and homing of human CD34+ cells to the bone marrow compartment. AMD3100 is a small molecule which potently inhibits SDF-1 binding and signalling via CXCR4 and affects the rapid mobilization of peripheral blood progenitor cells from marrow to blood in humans. The discovery, development and clinical use of AMD3100 administered alone and in combination with G-CSF for mobilization of progenitor cells will be presented.

**Gary Bridger**

Vice-President, Research and Development & Chief Scientific Officer, AnorMED Inc., Langley, British Columbia, Canada

Vice-President Research and Development & Chief Scientific Officer Dr. Bridger is a founding member of AnorMED. He is responsible for leading the Company's research and development activities including the initiation of new projects as well as providing scientific support to ongoing clinical and development programs. Dr. Bridger has been instrumental in building the Company's research group from its inception to its current complement of over 70 scientists. Prior to joining AnorMED, Dr. Bridger played a leading role in all aspects of chemistry research for Johnson Matthey's biomedical research group. In 1987, he received a Ph.D. in Chemistry from the University of Manchester Institute of Science and Technology (U.K.) and did post-doctoral research at Boston College.

**Discovery of novel leads in a biotechnology datastream.**

Thomas Gadek, SARcode, Oakland, California, USA

Recent advances in structural biology and genomics have enabled the rational identification of novel small molecule leads targeting proteins and gene products linked to human diseases. Several case studies will be discussed where structure activity relationships have been developed for a protein target's cognate protein ligand. This information has been used to recast that protein SAR into a parallel SAR for novel small molecule leads.

Thomas Gadek

Founder and CSO, SARcode, Oakland, California, USA

Dr. Gadek has been involved in defining Genentech's approach to small molecule lead identification over the last 15 years. He has utilized alanine point mutagenesis and conformationally defined peptides to identify the binding epitopes of proteins and then designed small molecules which are capable of mimicking these protein/peptide epitopes. This work has been particularly effective in blocking large protein-protein interactions including GPIIbIIIa/fibrinogen, alpha-V/beta-3/vitronectin and LFA-1/ICAM. Currently, Dr. Gadek is involved in a start-up biotech company which seeks to capitalize on these efforts in the oncology arena. Dr. Gadek received his PhD. from the University of California at Berkeley, and has published extensively on the inhibition of protein-protein interactions. He has authored more than 50 peer reviewed articles and is an inventor on more than 70 patent applications.

**SESSION 2**

**Special considerations in formulating new  
chemical entities derived from biotechnology.**

*(cosponsored by the International Liposome Society)*

**Pieter Cullis**

Inex Pharmaceuticals Corporation, Burnaby, British Columbia, Canada

Pieter R. Cullis, Ph.D., Professor, Department of Biochemistry and Molecular Biology, University of British Columbia; Chief Scientific Officer and Senior Vice President, Research, Inex Pharmaceuticals Corporation. Dr. Cullis came to UBC in 1978 and was a Scholar of the Canadian Medical Research Council (MRC) (1978-1983) and subsequently an MRC Scientist (1983-1988). His research has been focused on understanding the roles of lipids in biological membranes and the utility of "model membrane" systems for drug delivery. His laboratory has been responsible for fundamental advances in the generation, loading and targeting of lipid-based systems for intravenous delivery of conventional and genetic drugs. This work has led to two products that have been approved by regulatory agencies for the treatment of cancer and its complications. From 1987 to 1991, Dr. Cullis was President and Director of The Canadian Liposome Company Inc. (CLC), a company he co-founded. CLC was a subsidiary of The Liposome Company Inc. (TLC), a public company based in Princeton, New Jersey that was acquired by Elan plc in 2000. Dr. Cullis has also played a founding role in Inex Pharmaceuticals Corp., Lipex Biomembranes Inc. (Director and Chairman, 1985-2000), Northern Lipids Inc. and Protiva Biotherapeutics Ltd. (Director and Chairman, Scientific Advisory Board). Dr. Cullis is also a Director of Synapse Technologies Ltd. He has published over 250 scientific articles and is an inventor on over 30 patents. Dr. Cullis was awarded the Ayerst Award by the Canadian Biochemical Society in 1986, the B.C. Science Council Gold Medal for Health Sciences in 1991, the international 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.

**Theresa M. Allen**

Professor of Pharmacology and Oncology, Faculty of Medicine, University of Alberta, Edmonton, Alberta, Canada

Theresa Allen is a professor of Pharmacology and an adjunct professor of Oncology at the University of Alberta. She has been active in the drug-delivery field for over 25 years and has made important contributions to the development of long-circulating liposomes and to the development of ligand-targeted liposomal carriers for anticancer drugs and gene medicines. She has 200 peer-reviewed publications and is an inventor on several patents, which have resulted in three products, approved either for marketing or in clinical trials. She is frequently an invited speaker at international conferences has received a number of awards including the Novartis award from the Pharmacological Society of Canada for significant contributions to the advancement and extension of knowledge in Pharmacology; the ASTech Award for Leadership in Alberta Technology and the Alec Bangham International Award for contributions to liposome research.

## Considerations for the Development of Nucleic Acid Based Drugs

Ian MacLachlan, Protiva Biotherapeutics Inc.,  
Burnaby, British Columbia, Canada

Modern biotechnology has produced novel nucleic acid molecules with therapeutic potential; however, many of these compounds cannot be effectively delivered *in vivo* using current drug delivery techniques. Recently, a number of liposomal systems have been designed for the delivery of conventional drugs (including chemotherapeutic agents and antibiotics), several of which have shown promise in the treatment of cancer and are now either in clinical trials or approved for use in humans. These successes point to the desirability of developing liposomal systems for the *systemic* delivery of nucleic acid drugs. Unfortunately, techniques that had proven useful for loading weakly basic small molecule drugs into vesicles are unsuited to the encapsulation of polynucleotides. Here we describe an approach to encapsulation that allows for the incorporation of multi-gram quantities of polynucleotide in a serum stable particle under GLP or GMP conditions. Minor changes in the composition of the lipid bilayer allow for the encapsulation of plasmid DNA, siRNA, transcription factor decoys and other nucleic acid drugs. This method results in small (~100 nm diameter) uniform particles containing the nucleic acid payload fully encapsulated within a lipid bilayer stabilized by the presence of a polyethyleneglycol (PEG) coating. Evaluation of the pharmacokinetics of plasmid containing particles (SPLP) confirms a correlation between the residency time of the PEG-lipid component, extended circulation and the pattern of tumor specific gene expression that results from intravenous administration. SPLP accumulate in tumors to levels corresponding to 10% of the total injected dose per gram of tumor (greater than 1000 copies of plasmid DNA per tumor cell), representing a  $\sim 10^6$  and  $\sim 10^3$  fold improvement over free plasmid DNA or lipoplex systems respectively. The resulting pattern of gene expression reveals a preferential transfection of tumor cells vs. non-target tissue, gene expression in the tumor is more than two orders of magnitude greater than that observed in any other tissue including the so-called first pass organs such as the liver, lung and spleen. These results confirm that small uniform size, low surface charge and extended circulation lifetimes are prerequisite to vector accumulation and expression in tumors following systemic administration. Furthermore, they compare favourably to the degree of specificity exhibited by other so-called 'targeted' therapeutics such as antibodies or immunoconjugates and illustrate the potential for the development of exquisitely specific nucleic acid-based anti-tumor strategies. SPLP are the subject of an ongoing Phase I clinical trial treating late stage melanoma. Early trial results will be discussed, including those that have implications for the development of other nucleic acid based drugs.

### Ian MacLachlan

Chief Scientific Officer, Protiva Biotherapeutics Inc.,  
Burnaby, British Columbia, Canada

Ian MacLachlan, Ph.D., Chief Scientific Officer, Protiva Biotherapeutics Inc. Dr. MacLachlan is responsible for leading Protiva's research and development activities, as well as providing scientific support to ongoing clinical programs. Dr. MacLachlan has been active in the gene delivery field for more than a decade. A graduate of the University of Alberta, where he received his B.Sc. and Ph.D. in Biochemistry, he spent two years at the Vienna Bio-Center where some of the first experiments in systemic gene transfer were performed prior to conducting 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. He co-founded Protiva after spending five years leading the development of the SPLP technology at Inex Pharmaceuticals. Dr. MacLachlan has been an invited speaker at the National Institutes of Health, the National Cancer Institute, numerous academic institutions and most major scientific meetings dealing with gene transfer.



**Design of Novel Biocompatible,  
Biodegradable Materials Based on  
Consideration of Polymer-Drug Miscibility.**

**Christine Allen**, Pharmaceutical Sciences, Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, Ontario, Canada

The integration of polymers into a technology platform brings unparalleled diversity owing to the ability to synthesize new and exciting materials. However, with that said there is a scarcity of biodegradable, biocompatible polymers approved for use in medical applications. In addition, formulation development often occurs by trial and error with no clear method of predicting which polymer is best suited to formulate a specific drug. Our laboratory has recently begun using an integrated approach including computer modeling to guide prediction of polymer-drug compatibility and interaction. The findings from compatibility studies are then used to guide our synthetic and formulation efforts. Compatibility between drug and polymer is known to be one of the key factors in determining the effectiveness of polymeric delivery systems. Herein we consider compatibility between a polymer and drug to refer to miscibility and /or interaction with no alteration in the chemical structure of the polymer or the drug. Since each drug has its own unique chemical and physical properties, no delivery vehicle prepared from a particular polymer will serve as a universal carrier for all drugs. The degree of compatibility between polymer and drug has already been shown to be of importance in the design of a wide range of delivery systems including block copolymer micelles, nano or microparticles, films and gels. Specifically, compatibility or degree of interaction between polymer and drug affects many of the performance related characteristics of the delivery system including stability, drug loading capacity, drug loading efficiency and drug release kinetics. To this point, our studies have shown that an integrated approach may be used to reliably predict polymer-drug compatibility. Our findings also confirm that material selection based on consideration of polymer-drug compatibility allows for design of effective formulations for specific drugs.

**Christine Allen**

Assistant Professor, Pharmaceutical Sciences, Leslie Dan Faculty of Pharmacy, University of Toronto, Ontario, Canada

Dr. Christine Allen joined the Faculty of Pharmacy in July of 2002. She is cross-appointed in the Departments of Chemistry and Chemical Engineering and is the Associate Director of the Molecular Design and Information Technology Center. Her research is focused on the rational design and development of new materials and technologies for the delivery of anti-cancer agents. Allen completed her doctoral research at McGill University in the Department of Chemistry, focusing on the physico-chemical characterization of block copolymer micelles for applications in drug delivery. Following her PhD, she was awarded NSERC and Killam postdoctoral fellowships, which she used to pursue research on both polymer (Faculty of Pharmaceutical Sciences, UBC) and lipid-based (Department of Advanced Therapeutics, B.C. Cancer Agency), drug delivery systems for cancer treatment. She joined the Faculty from Celator Technologies Inc. of Vancouver, a company that grew out of the B.C. Cancer Agency, where she worked as the Assistant Director of Materials Research. She has publications, patent applications and review articles on both lipid and polymer-based delivery systems. Currently, she teaches physical chemistry and pharmaceuticals.

## Formulation and delivery of oligonucleotides for immunotherapy

Michael J. Hope, Inex Pharmaceuticals Corporation, Burnaby, British Columbia, Canada

Inex employs a liposome-based, targeted chemotherapy platform to encapsulate and deliver therapeutic compounds through the bloodstream to tumor sites. We have formulated a number of antisense oligonucleotides (ODN) for intravenous delivery and demonstrated enhanced efficacy compared to the free drug. However, the antitumor activity observed for Inex's antisense phosphorothioate (PS) ODN targeting the *c-myc* protooncogene correlates better with an immune mechanism than it does with an antisense mechanism of action. The therapeutic benefit from PS ODN containing immune stimulatory sequences (ISS) has been demonstrated in a variety of animal models of cancer and infection. In particular, when CpG-containing PS ODN are administered to mice, activation of macrophage/monocytes, dendritic cells, NK cells, T cells and B cells occurs, resulting in the release of an array of cytokines including IL-12, IFN- $\gamma$ , IL-6, IL-10 and TNF- $\alpha$ . When CpG-containing ODN are formulated with lipids and administered intravenously to ICR mice the plasma concentrations of IL-12, IFN- $\gamma$ , IL-6, MCP-1 and TNF- $\alpha$  are greatly increased compared to the same dose of free ODN. Furthermore, when phosphodiester (PO) ODN is substituted for PS ODN in the formulation cytokine induction is even greater at the early time points. This is in marked contrast to free PO ODN, which is inactive. As well as exhibiting non-specific bioresponse modifier effects when administered intravenously, these formulations can be mixed with, or covalently coupled to, antigens to boost humoral and cellular immune responses following subcutaneous administration. Therapeutic applications of this platform technology in cancer and infectious diseases will be discussed.

Michael J. Hope

Principal Scientist, Inex Pharmaceuticals Corporation, Burnaby, British Columbia, Canada

Dr. Michael Hope is Principal Scientist at Inex Pharmaceuticals Corporation, Burnaby, British Columbia, Canada. Inex employs a liposome-based, targeted chemotherapy platform to encapsulate and deliver therapeutic compounds through the bloodstream to tumor sites. Inex's lead product candidate, called Onco TCS, is a liposomal formulation of the widely used oncology drug vincristine. On March 15, 2004, Inex completed the filing of a New Drug Application with the US Food and Drug Administration seeking marketing approval for Onco TCS as a single-agent treatment for patients with relapsed aggressive non-Hodgkin's lymphoma. Dr. Hope is one of the founding scientists of Inex, which was formed in 1992 to develop drug delivery technology developed in the Department of Biochemistry and Molecular Biology at the University of British Columbia (UBC). Prior to this, he was a Vice President of the Canadian Liposome Company, Assistant Professor in the Division of Dermatology, Department of Medicine at UBC and a Director of the Liposome Research Unit (LRU), a network of drug delivery research groups in Vancouver. His research background is in the field of lipids and their role in membrane structure and function and the therapeutic applications of liposome technology. Dr. Hope received his Ph.D. in Biochemistry from the Royal Free Hospital School of Medicine, University of London (UK) in 1976 and did his post-doctoral training in the Department of Biochemistry, University of Utrecht, The Netherlands.

**Antibody-mediated targeting of antiproliferative antisense oligonucleotides in vitro and in vivo.**

Theresa M. Allen, Faculty of Medicine, University of Alberta, Edmonton, Alberta, Canada

Genomics and proteomics research frequently result in peptide- or nucleic acid-based drugs that have difficulties in reaching in vivo targets. Hence, there is an urgent need to develop innovative drug delivery technologies that will improve the in vivo delivery of these types of compounds, both in terms of efficiency and selectivity. The current viral and lipoplex delivery systems lack target selectivity and cationic lipid complexes have poor pharmacokinetics (PK). We have developed novel formulations for in vivo delivery of plasmid DNA, antisense oligonucleotides (asODN) or siRNA, termed coated cationic liposomes (CCL). CCL are surface neutral particles that have trapping efficiencies for asODN of over 90%, and circulation half-lives of several hours. Selective binding to target cells is mediated through antibodies or ligands coupled to the surface of the CCL. Anti-GD<sub>2</sub>-targeted CCL containing asODN against the c-myc proto-oncogene was used in the treatment of a xenograft model of metastatic melanoma. Significant down-regulation of the growth of the primary tumor was observed and tumor metastases were almost completely eliminated from animals treated with the targeted CCL[c-myc asODN], compared to various control groups. Down-regulation of the c-myc protein could be demonstrated in tumor tissue and cell death was due to apoptosis.

**Theresa Allen**

Professor of Pharmacology and Oncology, Faculty of Medicine, University of Alberta, Edmonton, Alberta, Canada

Theresa Allen is a professor of Pharmacology and an adjunct professor of Oncology at the University of Alberta. She has been active in the drug-delivery field for over 25 years and has made important contributions to the development of long-circulating liposomes and to the development of ligand-targeted liposomal carriers for anticancer drugs and gene medicines. She has 200 peer-reviewed publications and is an inventor on several patents, which have resulted in three products, approved either for marketing or in clinical trials. She is frequently an invited speaker at international conferences has received a number of awards including the Novartis award from the Pharmacological Society of Canada for significant contributions to the advancement and extension of knowledge in Pharmacology; the ASTech Award for Leadership in Alberta Technology and the Alec Bangham International Award for contributions to liposome research.

### SESSION 3

**Analytical issues related to  
synthetic and biotech-derived molecules.**

*(cosponsored by the Calibration Validation Group)*

**Gordon McKay**

CEO, PharmaLytics Inc., Saskatoon, Saskatchewan, Canada

Dr. Gordon McKay received his BSc and Ph.D. degrees in biochemistry from the University of Saskatchewan. After a brief postdoctoral training period in pharmaceutical science, he was appointed as a research associate and adjunct professor of pharmacy in the College of Pharmacy at the University of Saskatchewan and a principal investigator in the Drug Metabolism, Drug Disposition Research Group headed by Dr. Kamal K. Midha at this same institution. The research group received the first program grant awarded by the Medical Research Council to a College of Pharmacy and the first ever awarded to the University of Saskatchewan. This research was renewed for a total of 11 years after which the group began to focus on collaborative research with the pharmaceutical industry and has continued in this regard for almost 25 years. Dr. McKay was awarded fellowship in the American Association of Pharmaceutical Sciences in 1994 for his original contributions to pharmaceutical analysis and was one of the founding members of the Canadian Society of Pharmaceutical Sciences on whose executive he is now the President. He is a scientific organizer for numerous scientific meetings including the Bioanalytical Validation meetings, the Tandem Mass Spectrometry Workshops held annually for the last 15 years and BioInternational. He has served on the editorial board for J.Pharm.Sci. and has been a member of the Pharmaceutical Sciences review committee for MRC and has served on numerous University Boards and Committees. Dr. McKay has published more than 165 original scientific publications and authored more than 200 scientific presentations. Currently he is the chief executive officer for a new not for profit research institute at the University of Saskatchewan which is focused on collaborative research with the pharmaceutical industry aimed at discovering, developing and training in the areas of pharmaceutical science.

**Yiu-Chung Lee**

Director, Analytical Development, Patheon Incorporation Inc., Mississauga, Ontario, Canada

Dr Y.C. Lee is the Director of Analytical Development at Patheon Incorporation. Patheon is a leading global provider of outsourced drug development and manufacturing services to pharmaceutical and biotechnology companies. Between 1991 to 2002, Dr Lee was a Research Scientist in the Lilly Analytical Research Laboratory at Eli Lilly Canada Inc. He has more than 15 years of analytical development experience in method development, method validation, experimental design, drug product specifications and stability testing. He is one of the editors of the book "Analytical Method Validation and Instrument Performance Verification" published by Wiley. Dr Lee is one of the founders of the Calibration & Validation Group (CVG). CVG is a non-profit organization formed by more than 1,500 analytical and formulation scientists from the pharmaceutical and chemical industries, academia and government agencies across Canada.

## Quantitative Analysis of Bio-Technologically Derived Pharmaceutical Product by LC-MS/MS

Fabio Garofolo and Luigi Colombo, Vicuron Pharmaceuticals Inc., Gerenzano (VA), Italy

LC-MS/MS and Microbiology assays are two leading techniques employed in the analysis of natural antibiotics. Microbiology assays measure the real activity (potency) present in the sample. They provide better quantitative evaluation of microbiological active multi-components drugs, more significant data for PK/PD evaluation, easier sample preparation, and lower cost per sample than LC-MS/MS assays. On the other hand Microbiology assays are more compound-dependant and less specific (usually not applicable when different microbiological active drugs are co-administered) than LC-MS/MS assays. The advantaged and disadvantages of LC-MS/MS and microbiology assays have been demonstrated considering the following examples: quantification of a new natural antibiotic in biological fluids in presence of its metabolite, and activity vs. concentration in the analysis of ramoplanin degradation products. The class of natural antibiotics that was studied belongs to the glycopeptides class of second generation. It shows a better antibacterial activity, pharmacokinetic, and tolerability profile than teicoplanin and vancomycin. The development and validation of a reliable quantitative method of this class of compounds are extremely challenging due to the high molecular weight (around 2000 Dalton), stickiness, and mainly multi-components nature (Complex Drug) of natural antibiotics. Indeed, the drug itself is constituted by some main components and many minor components. Conventional methods and criteria used for the LC-MS/MS quantitative bioanalysis of synthetic drugs from plasma and urine usually fails when used to quantify these compounds. Therefore, innovative and specific bioanalytical strategies were developed to overcome the analytical problems. Corresponding author: Dr. Fabio Garofolo, Bioanalysis & PK Head, Vicuron Pharmaceuticals Inc., Via R. Lepetit, 34, I-21040 Gerenzano (VA), Italy. fgarofolo@vicuron.it

Fabio Garofolo

Bioanalysis and PK Head, Vicuron Pharmaceuticals Inc., Gerenzano (VA), Italy

Dr. Fabio Garofolo has been involved in High Performance Liquid Chromatography (HPLC), Gas Chromatography - Mass Spectrometry (GC-MS) and mainly Liquid Chromatography - Tandem Mass Spectrometry (LC-MS/MS) for more than 13 years. He is specialized in applications of LC-MS in FORENSIC, ANALYTICAL and BIOANALYTICAL fields. Dr. Garofolo has been involved in teaching LC-MS since 1995. He is the official LC-MS instructor for the Calibration and Validation Group in Canada. He has developed a multilevel LC-MS course focused on "High Throughput LC-MS/MS and Advance Method Development". Capitalizing on an extensive occupational background within his specialization field, he provides innovative solutions and specific training for fast method development in LC-MS. At present is leading the Bioanalysis and PK Department at Vicuron Pharmaceuticals Inc., an international biopharmaceutical company focused on discovering, developing, manufacturing and commercializing vital medicine for seriously ill patients. Career Steps: Bioanalysis & PK Head, Vicuron Pharmaceuticals Inc. (Present). President, LC-MS Pharmaceutical Development Inc. (Present), Technical Manager, Eli Lilly Canada (2000-2002); Laboratory Director/Leader of the Method Development Group, Biovail Contract Research Canada (1998-2000); Laboratory Director, R&D Dept.-Analytical Laboratory, Italian Air Force Italy (1994-1998). Accomplishments: 13 years of experience in Method Development. 36 Publications & Presentations in International Conferences. 93 Innovative Bioanalytical and Analytical Methods Developed and Validated. Author and instructor of 23 LC-MS courses from Basic to Advance level. Designer and inventor of 3 innovative bioanalytical approaches: Universal Bioanalytical Method theory (UBM) and TFC coupled with High Flow Normal Phase (TFC-HF-NPLC-MS/MS), IPA/Acid Ionization approach for natural antibiotics. 11 years of extensive managerial and technical experience of laboratories and departments of up to 50 personnel. Education: Specialization in Behavioral Medicine and Health Psychology – Doctor's Degree in Psychology, Northcentral University, USA (in progress). Advanced Management, York University, Canada (1998-2000). Specialization in Meteorology, Aeronautica Militare – Doctor's Degree in Chemistry, Università degli Studi di Roma "La Sapienza" -Italy (1985-1994)

### **Proteomics analysis of the detoxification machinery in rat hepatic endoplasmic reticulum**

Alexander W. Bell, Data Interpretation Unit, Montreal Proteomics Network, McGill University, Montreal, Ontario, Canada

Proteomics analyses of highly enriched preparations of the male rat hepatic endoplasmic reticulum was done from 2-D and 1-D gels followed by LC-QToF tandem MS, as well as 2D-LC-QTrap, 2D-LC-Ion Trap and LC-FTICR MS. Endoplasmic reticulum rough and smooth microsome fractions were characterized by a combination of marker enzyme assays, Western blotting and electron microscopy. A maximum of 39 different cytochrome P450 proteins were characterized by LC-QToF MS analysis of the 46 to 57 kDa (6 bands) region from a 1D gel while a minimum of 29 different cytochrome P450 paralogues were found by 2D-LC MS analysis of the corresponding pool. In addition, allelic isoforms of six of the cytochrome P450 proteins were characterized. Abundance of each cytochrome P450 was estimated with P450s involved in steroid metabolism (10) or inducible P450s (14) representing 40 and 35% of the total P450 protein. The rat genome has identified 64 potential coding genes. Proteomics has conclusively characterized 33 with their relative abundance estimated. In addition exhaustive mass spectrometry analysis of 1-D gels by LC-QToF tandem MS characterized 12 glucuronosyl transferases, 10 carboxylesterases and 12 dehydrogenase enzymes involved in detoxification. In addition, the cytochrome P450 reductase and glutathione S-transferase proteins were characterized. This represents the most complete analysis of proteins involved in metabolic detoxification serving as an important base for understanding human drug metabolism.

### **Alexander Bell**

Team Leader/Professional Associate, Data Interpretation Unit, Montreal Proteomics Network, McGill University, Montreal, Ontario, Canada

Dr. Bell (Doctor of Philosophy, University of Manitoba) is in the Montreal Proteomics Network, McGill University. He joined McGill University in 1990 in the Sheldon Biotechnology Centre and then in 1995 joined the Department of Anatomy and Cell Biology. His research interests focus on protein characterization at the molecular level including post-translational modifications and mass spectrometry. Currently, he is involved in high throughput proteomics and discovering the total CellMap of all proteins in the mammalian cell. He has co-authored over 40 papers, has been an invited speaker at several conferences, and has been involved in the training of more than 10 graduate students. Since joining Dr. John J.M. Bergeron in the Department of Anatomy and Cell Biology, he has been directly involved in several successful Canada Foundation for Innovation (CFI) and Genome Canada grant applications that have been the foundations for the Montreal Proteomics Network. He lectures in proteomics.

## Novel Hybrid Mass Spectrometer Systems for Pharmaceutical Research and Development

Bori Shushan, New Business Development, MDS Sciex, Concord, Ontario, Canada

Applied Biosystems-MDS SCIEX introduced linear ion trap (LIT) technology two years ago configuring it into a triple quadrupole analyzer as a hybrid quadrupole-LIT tandem mass spectrometer system called the QTrap. Since then many useful qualitative and quantitative applications of this technology have been developed for pharmaceutical and biopharmaceutical R&D. The QTrap system combines the high sensitivity and dynamic range of the triple quadrupole and the high duty cycle and speed of ion trapping technology in a single instrument. Furthermore, the system is capable of many new scan modes heretofore unavailable to either triple quadrupole or ion trap analyzers alone. One application of these combined strengths will be the demonstration of significantly better detection limits for pharmaceuticals in complex biological matrices using MS<sup>3</sup>. The combination of conventional collision induced dissociation (CID) of the triple quadrupole and resonant excitation CID of the LIT is unique feature of the QTrap. Along with the increased transmission efficiency of the LIT over conventional ion trap technologies, we were able to demonstrate the sub-pg/mL detection of pharmaceuticals in crude protein-precipitated plasma using LC-MS<sup>3</sup>. The many compound-specific scan modes available on the QTrap are rapid enough to be useful in monitoring a significant number of compound classes during the analysis of complex mixtures. When a member of a target compound class is detected, more detailed product ion scans are automatically initiated for identification of the species of interest; this approach is useful in drug metabolism studies or in the characterization of post-translationally modified proteins. We will also demonstrate the use of isotope-dilution nano-LC-MS/MS in the analysis of ideotypic tryptic peptides for the rapid and flexible quantitation of protein-based biomarkers. Such analyses can be made at the low to sub fmole levels suitable for biomarker validation studies requiring the high throughput analysis of many samples.

Bori Shushan

Manager, New Business Development, MDS Sciex, Concord, Ontario, Canada

Dr. Shushan received his Ph. D. from the Guelph-Waterloo Centre for Graduate Work in Chemistry in Analytical Chemistry specializing in Tandem Mass Spectrometry in 1980. He joined MDS SCIEX that same year and worked in R&D on the development of applications for MDS SCIEX' novel atmospheric-pressure ionization tandem mass spectrometer system. In his 24-year career at MDS SCIEX, Dr. Shushan has key positions in Application Research and Development, Marketing and Sales, Technical Marketing and Sales Support. He is now responsible for New Business Development for MDS SCIEX where he evaluates and develops new technologies for MDS SCIEX to commercially exploit particularly in the area of Pharmaceutical and Life Sciences.



**Consensus Guidelines for the Development and Validation of Immunochemistry Assays for Pharmacokinetic Studies of Macromolecules.**

**Russell S. Weiner**, Clinical Discovery-Immunology, Bristol-Myers Squibb, Princeton, New Jersey, USA

Immunochemistry based assays (EIA, RIA, etc.) are the method of choice for quantifying macromolecule therapeutics in pharmacokinetic samples derived from non-clinical and clinical studies. However, there currently does not exist harmonized bioanalytical methods validation guidance specifically aimed at this class of assays. To best facilitate the creation of such guidance, based on strong scientific principles, a diverse committee comprised of individuals from Pharma, Biotech, and CRO organizations have developed a best practices document. This document specifically describes a standardized approach for method development, pre-study and in-study validation of quantitative immunoassays for macromolecules. Recommendations arising from this consensus-based approach should have the best opportunity of being considered by regulatory agencies in their development of appropriate guidance. This presentation will address the critical assay parameters that should be evaluated including: range, accuracy, precision, quantitation limit, stability, specificity, linearity, robustness, cross-validation, prozone/hook effect, and dilution linearity.

**Russell Weiner**

Associate Director, Clinical Discovery-Immunology, Bristol-Myers Squibb, Princeton, New Jersey, USA

Dr. Weiner is currently an Associate Director in the Department of Clinical Discovery- Immunology where he is responsible for the clinical development of therapeutics for inflammatory diseases. He received his B.S. in Biochemistry from the State University of New York at Stony Brook and a Ph.D. from Albany Medical College. Dr. Weiner joined Bristol-Myers Squibb in 1993 where he directed the research of both immunochemistry and mass spectrometry based bioanalytical groups. These groups supported method development, validation and sample analysis from discovery and clinical studies. This includes quantitative assays of protein and small molecule based therapeutics as well as biomarkers. Currently, he has taken on the responsibility of moving lead compounds from discovery through early clinical development including both proof-of-principle and mechanism of action studies. Dr. Weiner was part of a team of scientists comprised of members from large Pharma, Biotech, and CROs that developed guidelines for bioanalytical method validation of ligand-binding assays to support pharmacokinetic assessments of macromolecules. The recommendations of this team were the subject of a recent publication (Pharmaceutical Research 20:1885-1900 2003). He is an active member on several committees and focus groups of the American Association of Pharmaceutical Scientists including the Bioanalytical Focus Group, the Ligand Binding Bioanalytical Focus Group and the Biotech Section. Dr. Weiner has co-chaired several bioanalytical workshops and scientific conferences all focusing on method development and validation of assays to support the quantitation of protein therapeutics and biomarkers. russell.weiner@bms.com

#### SESSION 4

Special topics in pharmacokinetics and drug metabolism: small synthetic and biotech-derived entities.

**Micheline Piquette-Miller**

Associate Professor, University of Toronto, Toronto, Ontario, Canada

Micheline Piquette-Miller is an Associate Professor of Pharmacy and Pharmaceutical Sciences at the University of Toronto. She studied Pharmacy as an undergraduate and received her Ph.D. in Pharmacokinetics (1994) at the University of Alberta (supervisor: Dr. Jamali). Micheline completing a Post-Doctoral Fellowship in the area of molecular pharmacology (supervisor: Dr. Giacomini) at the University of California in San Francisco, then joined the University of Toronto in 1996. She presently teaches in the areas of pharmacokinetics; topics in pharmaceutical industry and drug development. Dr. Piquette-Miller's research examines the cellular and molecular basis for variability in drug response. Specifically, this has focused on understanding the mechanisms responsible for alterations in the expression of drug transport proteins and their resulting impact on drug disposition. This work is used to solve critical issues in chemo-responsiveness of tumors, variable drug response and prediction of drug-disease interactions. Micheline Piquette-Miller is a member of numerous national and international societies and serves as a reviewer for a number of pharmaceutical journals and granting agencies. She presently serves as Chair of the Pharmacogenetics and Molecular Pharmacology section of ASCPT, on the Board of Directors of the Canadian Society of Clinical Pharmacology and is on the Executive Council of the Canadian Society of Pharmaceutical Scientists. She has also been the recipient of several awards including the Rx &D Health Research Foundation-CIHR Research Career Award (2000), the Alberta Women's Science Network "Mentor of the Millennium" (2000), the Pfasky Young Investigator Award (2003), and the University of Alberta Horizon Award (2003).

**Dion Brocks**

Associate Professor, University of Alberta, Edmonton, Alberta, Canada

Dr. Dion Brocks, who was elected Member at Large of CSPS in 2003, received is holder of BSc., B.Sc.(Pharm), M.Pharm. (Clinical pharmacy), and PhD. degrees, all received from the University of Alberta. Prior to commencing his academic career, Dr. Brocks worked as in hospital and community pharmacies in Alberta, and after receipt of his M.Pharm. degree, as Clinical Coordinator at the Rockyview Hospital Pharmacy department in Calgary. He received his doctoral degree in Pharmaceutical Sciences, specializing in Pharmacokinetics, in 1993. Dr. Brocks 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 suburban Los Angeles as Associate Professor of Pharmaceutical Sciences. He taught pharmacokinetics and pursued his research interests there until January 2002, when he returned to his alma mater as Associate Professor of Pharmaceutical Sciences. Dr. Brocks has published over 45 peer-reviewed manuscripts related to pharmacokinetics, and has numerous published abstracts and some book chapters. He has served as a member of the editorial board of the Journal of Clinical Pharmacology since 1996, has served as a peer reviewer for a number of journals in the pharmaceutical sciences. His current research interests lie in the study of stereoselectivity, and the effects of lipoproteins, on the pharmacokinetics of drugs. Dr. Brocks' research endeavours are currently funded by a grant from the Canadian Institutes of Health Research.

### **Impact of the pharmacologic target on the disposition of therapeutic proteins.**

**Charles B Davis**, Preclinical Drug Discovery, Microbial, Musculoskeletal and Proliferative Diseases, Center of Excellence for Drug Discovery, GlaxoSmithKline Research & Development, Collegeville, Pennsylvania, USA

Significant diversity in the pharmacokinetics of therapeutic proteins derives from diversity in their pharmacologic targets. Whereas the distribution of traditional small molecule therapeutics may be influenced by their targets in the event of a particularly high affinity, high specificity interaction, for protein therapeutics there is the potential for a significant impact on both drug distribution and drug elimination. Exposure to granulocyte colony-stimulating factor decreases with repeat dosing in patients as increasing neutrophils enhance clearance of the cytokine through binding, endocytosis and subsequent intracellular degradation of the ligand-receptor complex. Though many monoclonal antibodies (mAbs) have linear pharmacokinetics, low clearance and long half-lives, concentration and time-dependent pharmacokinetics have been observed as a consequence of the distribution, synthesis and degradation of the target antigen. Using transgenic and knockout mice, we have shown that the pharmacokinetics and tissue distribution of a mAb specific for CD4 on T lymphocytes are highly dependent on the presence and distribution of the target antigen. Subcutaneous bioavailability is dose-dependent as a consequence of pre-systemic antigen-antibody complexation in the lymphatic system. For an antibody specific for a soluble circulating coagulation factor, the rate of synthesis of the endogenous target controls the duration of anti-coagulant effect, since over time, increasing concentration of antigen saturates available antigen-combining sites. Studies of a novel human chemokine demonstrate the potential for off-target interactions to influence the disposition of a therapeutic protein. In this example, an erythrocyte antigen with significant homology to the pharmacologic target, and proteoglycans of the extra cellular matrix, independently affect the distribution of the chemokine. An understanding of the pharmacologic target provides considerable insight regarding the disposition of the therapeutic protein as well as factors that are likely to influence pharmacodynamics and clinical response.

**Charles Davis**

Director, Preclinical Drug Discovery, Microbial, Musculoskeletal and Proliferative Diseases, Center of Excellence for Drug Discovery, GlaxoSmithKline Research & Development, Collegeville, Pennsylvania, USA

A graduate of Swarthmore College (BA) and Cornell University (PhD), Dr Davis joined Drug Metabolism and Pharmacokinetics, SmithKline Beecham Pharmaceuticals, in 1989. He held various positions of increasing responsibility within DMPK and was appointed Associate Director, Clinical Pharmacokinetics in 1998. At the merger of Glaxo Wellcome and SmithKline Beecham, Dr Davis joined gsk's Centre of Excellence in Drug Discovery as Head of Preclinical Drug Discovery for Microbial, Musculoskeletal, Proliferative Diseases, Dermatology and Diseases of the Developing World. Dr Davis has contributed to more than 10 biologics and 10 small molecule investigational new drug applications.

### **Pharmacokinetics and Pharmacodynamics of Polysaccharide-Based Macromolecular Prodrugs.**

**Reza Mehvar**, School of Pharmacy, Texas Tech University Health Sciences Center, Amarillo, Texas, USA

New and innovative methods of delivery of therapeutic agents using polysaccharide as carriers have been recently developed, which target site of action, increase the intensity and/or prolong pharmacologic action, and/or reduce toxicity of small molecule drugs, proteins, or enzymes. The physicochemical properties of these carriers, including molecular weight (MW), electric charge, chemical modifications, and degree of polydispersity and/or branching would significantly affect in vivo disposition and pharmacodynamic profiles of drugs that are carried by these macromolecules. Generally, large MW polysaccharides (MWs  $\leq$  40 kD) have low clearance and relatively long plasma half-life, resulting in accumulation in reticuloendothelial or tumor tissues. The tumor accumulation in most cases is a passive targeting due to "enhanced permeation and retention" of macromolecules by tumors. Additionally, drugs such as anticancer agents may be actively targeted to specific cells by polysaccharides to which appropriate ligands are attached. The importance of pharmacokinetic considerations in the design and pharmacodynamics of polysaccharide-based macromolecular prodrugs will be demonstrated using a dextran-methylprednisolone conjugate as an example. Collectively, these data suggest that macromolecular polysaccharides are promising agents for improving drug delivery.

**Reza Mehvar**

Professor of Pharmaceutical Sciences, School of Pharmacy, Texas Tech University Health Sciences Center, Amarillo, Texas, USA

Reza Mehvar received his Pharm.D. (1979) from the University of Tehran College of Pharmacy (Tehran, Iran) and his Ph.D. (1988) in Pharmaceutical Sciences (Pharmacokinetics) from the University of Alberta Faculty of Pharmacy (Edmonton, Canada). In 1988, he joined Drake University College of Pharmacy in Des Moines, IA (USA) as an Assistant Professor of Pharmaceutics where he was eventually promoted to Professor of Pharmaceutics prior to joining Texas Tech School of Pharmacy in 1999. His laboratory research is currently focused on the pharmacokinetic-based delivery approaches for liver diseases, including liver ischemia-reperfusion damage and transplantation, and the role of liver in the disposition of xenobiotics. His research in this area has been funded by NIH, American Heart Association, and pharmaceutical industry. Additionally, he teaches pharmacokinetics courses for which he has received several awards, including two from the American Association of Colleges of Pharmacy.

## **Role of Carrier-mediated Transport Systems in the Optimization of Drug Delivery and Response**

**Micheline Piquette-Miller**, Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, Ontario, Canada

Carrier-mediated transport is an active research area in drug delivery today. This stems from the fact that many compounds require active carrier-mediated transport mechanisms in order to cross-epithelial barriers during the processes of absorption and distribution to sites of action. Furthermore, several relatively non-specific drug efflux transporters suppress oral absorption, hinder drug entry into brain and promote drug secretion for a large number of clinically important drugs. Indeed, a host of transporter proteins exist which can be targeted for improving epithelial drug absorption and distribution. Hence, linking carrier-mediated transport strategies to drug delivery has the potential to diminish the undesirable pharmacokinetic profiles of many drugs. One approach has been to modify or inhibit efflux transport systems such as P-glycoprotein. This method serves to enhance passive absorption or entry of drugs into cells and tissues. Moreover, the use of P-glycoprotein inhibitors has been extensively investigated as a method to overcome multidrug resistance of tumors. Another approach has been to chemically create prodrugs, which links a drug to an endogenous compound; allowing for recognition and cellular uptake by carrier mediated transporters. This method strives to increase drug absorption or cellular transport by exploiting nutrient uptake transporters such as the PEPT1 intestinal transporter. This talk will discuss several methods by which carrier-mediated transport systems have been targeted for optimizing drug delivery.

## **Micheline Piquette-Miller**

Associate Professor, Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, Ontario, Canada

Micheline Piquette-Miller is an Associate Professor of Pharmacy and Pharmaceutical Sciences at the University of Toronto. She studied Pharmacy as an undergraduate and received her Ph.D. in Pharmacokinetics (1994) at the University of Alberta (supervisor: Dr. Jamali). Micheline completing a Post-Doctoral Fellowship in the area of molecular pharmacology (supervisor: Dr. Giacomini) at the University of California in San Francisco, then joined the University of Toronto in 1996. She presently teaches in the areas of pharmacokinetics; topics in pharmaceutical industry and drug development. Dr. Piquette-Miller's research examines the cellular and molecular basis for variability in drug response. Specifically, this has focused on understanding the mechanisms responsible for alterations in the expression of drug transport proteins and their resulting impact on drug disposition. This work is used to solve critical issues in chemo-responsiveness of tumors, variable drug response and prediction of drug-disease interactions. Micheline Piquette-Miller is a member of numerous national and international societies and serves as a reviewer for a number of pharmaceutical journals and granting agencies. She presently serves as Chair of the Pharmacogenetics and Molecular Pharmacology section of ASCPT, on the Board of Directors of the Canadian Society of Clinical Pharmacology and is on the Executive Council of the Canadian Society of Pharmaceutical Scientists. She has also been the recipient of several awards including the Rx &D Health Research Foundation-CIHR Research Career Award (2000), the Alberta Women's Science Network "Mentor of the Millennium" (2000), the Pfiasky Young Investigator Award (2003), and the University of Alberta Horizon Award (2003) and Toronto Institute of Technology's Award of Excellence in Pharmaceutical Research (2003).

## Visualizing the pharmacokinetics and tissue distribution of novel biopharmaceuticals by molecular imaging techniques

Raymond M. Reilly, Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto General Research Institute, University Health Network, Toronto, Ontario, Canada

The pharmacokinetics of new drugs in humans has traditionally been determined through sampling biological fluids (blood, plasma, urine, CSF). These analyses provide important information on routes of excretion/metabolism and rates of elimination from the sampled compartments and the body, but do not directly provide insights on tissue disposition. Tissue disposition may be assumed from preclinical studies of the drug or implied by pharmacokinetic analyses. Single photon-emission computerized tomography (SPECT) and positron-emission tomography (PET) are molecular imaging techniques used in nuclear medicine that offer a unique opportunity to directly and non-invasively visualize the pharmacokinetics and tissue disposition of a new drug in humans. PET is the most useful for small drug molecules because the radionuclides used [ $^{11}\text{C}$ ,  $^{13}\text{N}$ ,  $^{15}\text{O}$  and  $^{18}\text{F}$ ] may replace an existing element in the structure with minimal or no perturbation of its physicochemical/pharmacological properties. The short half-life of PET radionuclides (2 mins-110 mins) is also feasible for small drug molecules that exhibit rapid kinetics of tissue accumulation and elimination. For most biopharmaceuticals (e.g. monoclonal antibodies and peptides), this is not the case, and SPECT is a more appropriate option. Biopharmaceuticals can be labeled for SPECT imaging by introducing metal chelators for  $^{99\text{m}}\text{Tc}$  or  $^{111}\text{In}$  into the proteins or by direct radioiodination with  $^{123}\text{I}$  or  $^{131}\text{I}$ . PET and SPECT have been used for many years in nuclear medicine to model the tissue uptake and elimination of radiopharmaceuticals, but the techniques are only now being recognized as revolutionary new tools for drug development. The advent of dedicated high-resolution small animal imaging gamma cameras (e.g. microSPECT and microPET) has extended the approach to preclinical drug development studies in animals. The technology of molecular imaging will be introduced with representative examples from the literature and from our current research aimed at the discovery and development of novel biopharmaceuticals for imaging and targeted radiotherapy of cancer.

## Raymond Reilly

Associate Professor, Leslie Dan Faculty of Pharmacy, University of Toronto and Scientist, Toronto General Research Institute, University Health Network, Toronto, Ontario, Canada

Dr. Reilly (BSc, pharmacy; MSc, nuclear pharmacy; PhD, medical biophysics, University of Toronto) is an Associate Professor at the Leslie Dan Faculty of Pharmacy and Department of Medical Imaging, University of Toronto and Scientist, Division of Clinical Investigation and Human Physiology, Toronto General Research Institute. He recently joined the faculty at the University of Toronto in 2003, after a career as nuclear pharmacist, first at Princess Margaret Hospital and then at the University Health Network, where he founded the Laboratory of Molecular Imaging and Targeted Radiotherapeutics (LMIR). His research interests are focused on the discovery and development of novel radiopharmaceuticals for molecular imaging and targeted radiotherapy of cancer, in particular breast cancer. He discovered a new radiopharmaceutical,  $^{111}\text{In}$ -labeled epidermal growth factor ( $^{111}\text{In}$ -hEGF), which acts as a "Trojan Horse" seeking out and destroying breast cancer cells displaying epidermal growth factor receptors (EGFR) through the emission of short-range Auger electrons in close proximity to DNA. He recently translated this discovery to the first clinical trial of the radiopharmaceutical in patients with advanced, chemotherapy-resistant breast cancer at Princess Margaret Hospital. He has published more than 60-refereed articles in the radiopharmaceutical sciences and his research program has received support from Canadian and U.S. granting agencies. His laboratory is an integral member of the Ontario Research and Development Challenge Funded, Center of Excellence in Breast Cancer Imaging Research. He has been a reviewer for nuclear medicine and pharmacy journals including the J. Nucl. Med., Nucl. Med. Biol., Cancer Biother. Radiopharm., J. Pharm. Sci. Can. J. Hosp. Pharm., Int. J. Radiat. Biol. and Clin. Cancer Res. as well as granting agencies including CIHR and CFI. His laboratory provides post-graduate training in radiopharmaceutical discovery and development and several of his students have won national and international awards for their thesis research. He contributes to undergraduate courses in pharmaceuticals and drug analysis and to graduate courses on radiopharmaceuticals.

## SESSION 5

Regulatory issues faced in development of  
small synthetic and biotech-derived entities.



**Brian Foster**

Senior Science Advisor, Office of Science, Therapeutic Products Directorate, Health Canada, Ottawa, Ontario, Canada

Dr. Foster is a Senior Science Advisor in the Office of Science, Therapeutic Products Directorate, Health Canada. He received his Ph.D. in Medicinal Chemistry at the University of Alberta in 1981 with Professor R.T. Coutts through research on alternative models for drug interactions and metabolism. Since joining Health Canada, his research has been in the areas of toxicology and drug disposition. His current research interest is in the area of drug disposition, pharmacogenetics, and how natural health products affect the safety and efficacy of conventional therapeutic products. Dr. Foster is an Adjunct Professor, Department of Cellular and Molecular Medicine, Faculty of Medicine, University of Ottawa where he has a joint Health Canada - University of Ottawa Centre for Research in Biopharmaceuticals and Biotechnology laboratory. He teaches graduate level courses on drug disposition and pharmacogenetics. <http://www.uottawa.ca/academic/med/cellmed/foster.html>

**Pollen Yeung**

Professor and Lab Director, Pharmacokinetics and Metabolism Laboratory, College of Pharmacy and Department of Medicine, Faculties of Health Professions and Medicine, Dalhousie University, Burbidge Building, Halifax, Nova Scotia, Canada

Pollen Yeung is currently Professor and Director of the Pharmacokinetics and Metabolism Laboratory, College of Pharmacy, Dalhousie University, Halifax, Nova Scotia, Canada. He obtained his undergraduate pharmacy degree (B.Sc. Pharm. 1979) and M.Sc. (1982) from the University of Manitoba, Winnipeg, Manitoba, and Ph.D. in pharmaceutical chemistry from the University of Saskatchewan (1986), Saskatoon, Saskatchewan. He joined the College of Pharmacy, Dalhousie University in Halifax, as an Assistant Professor in 1985, and was promoted to Full Professor in 1996. He also holds an adjunct appointment with the Department of Medicine at Dalhousie University and QEII Health Sciences Center. His research interests are in the area of pharmacokinetics, metabolism and pharmacogenomics of cardiovascular and anti-inflammatory drugs, and their effects on hemodynamic and neurohormone regulation that has received support from both government and pharmaceutical industry. He has served as a referee and consultant for many academic and professional organizations, pharmaceutical industry, government and granting councils. He is currently a member of the Expert Advisory Committee on Oncology Therapy for Health Canada, a member of the Board for BioNova, which is an industry association promoting biotechnology and life sciences industry in Nova Scotia and Atlantic Canada, and a member of the executive council (Treasurer) for the Canadian Society of Pharmaceutical Sciences (CSPS).

## **The Path and Strategies for the Development of Synthetic Small Molecules and Biotechnology-Derived New Drug Candidate**

David Kwok, BRI Biopharmaceutical Research Inc.,  
Vancouver, British Columbia, Canada

The path of proof-of-concept pharmacology studies leading to lead-candidate optimization and selection will be reviewed in this presentation. In context of today's business environment to succeed in the development of new drug candidates, the process of an accelerated pre-clinical development program will also be discussed. Analytical chemistry and toxicology techniques useful for drug candidate preclinical development are diverse and are constantly advancing. During this presentation, the design of analytical chemistry and toxicology studies useful for solving specific analytical chemistry and toxicology challenges during the preclinical development life cycle will be mentioned. This presentation is intended to provide an understanding of selected analytical chemistry / toxicology study strategies useful for overcoming specific development challenges in the development of both synthetic small molecule and biotechnology-derived drug candidates.

David Kwok

President and CEO, BRI Biopharmaceutical Research Inc., Vancouver, British Columbia, Canada

David Kwok is the founder and President of BRI Biopharmaceutical Research Inc., a contract research company established in 1999 with a mission to provide an integrated analytical and toxicology services to accelerate drug discovery and pharmaceutical product development in preclinical to phase-I. BRI routinely provides analytical services in in-vitro/vivo ADME screening studies, CMC studies, formulation development and development / validation of LC/MS/MS methods for biological samples. Dr. Kwok received his Ph.D. in 1991 from the Faculty of Pharmaceutical Sciences at the University of British Columbia. He served in a variety of management and scientific posts as a Research Scientist at the Therapeutic Products Program, Health Canada, involving herbal and botanical quality control method development, antimicrobial drug resistance and veterinary drug residues analytical methodologies.

## **Emerging regulatory issues: the Health Canada perspective**

**Brian Foster**, Therapeutic Products Directorate, Health Canada, Ottawa, Ontario, Canada

With the completion of the mapping of the human genome brings new hope in the discovery of new medicines, especially for diseases for which there is no treatment. There is stronger public demand for timely access to “safe” therapeutic products while at the same time provinces have to manage a fixed drug budget and therefore want a “bang for their buck.” With this hope for new products and safety awareness come new challenges for both the drug industry and the regulators. This talk will explore some of the safety issues, including what may be faced when pharmacogenetic information is used in the development of a new drug. A response to a drug is not consistent among patients in a population and in some cases is not consistent on a day-to-day basis within a patient. The pharmacogenetic component of the human is but one aspect in understanding a disease and its treatment, but perhaps more important is the understanding of the interactions of all the genetic components and their products. Pharmacogenetics also plays a role in the ADME of the drug, in the variation in the number and specificity of the receptors and on the other systems which are affected by the disease and the drug. The role of gender, ethnic differences and age may have to be explored in a different way when assessing efficacy and safety of drugs. The Canadian perspective will be presented together with some ICH guidance on this and some other regulatory issues.

**Brian C. Foster**

Senior Science Advisor, Office of Science, Therapeutic Products Directorate, Health Canada, Ottawa, Ontario, Canada

Dr. Foster is a Senior Science Advisor in the Office of Science, Therapeutic Products Directorate, Health Canada. He received his Ph.D. in Medicinal Chemistry at the University of Alberta in 1981 with Professor R.T. Coutts through research on alternative models for drug interactions and metabolism. Since joining Health Canada, his research has been in the areas of toxicology and drug disposition. His current research interest is in the area of drug disposition, pharmacogenetics, and how natural health products affect the safety and efficacy of conventional therapeutic products. Dr. Foster is an Adjunct Professor, Department of Cellular and Molecular Medicine, Faculty of Medicine, University of Ottawa where he has a joint Health Canada - University of Ottawa Centre for Research in Biopharmaceuticals and Biotechnology laboratory. He teaches graduate level courses on drug disposition and pharmacogenetics. <http://www.uottawa.ca/academic/med/cellmed/foster.html>

## SESSION 6

Roundtable discussion: pharmaceutical scientists  
and society: is the supply meeting the demand?

**Frank Abbott**

Executive Director of AFPC/ADPC  
Vancouver, British Columbia, Canada

Dr. Frank S. Abbott, B.S.P., Saskatchewan (1959); M.Sc., Saskatchewan (1962); Ph.D., Purdue (1966); Associate, Dept. of Pediatrics, Faculty of Medicine (1988-present), is currently Professor and Dean Emeritus of the Faculty of Pharmaceutical Sciences at the University of British Columbia. He was a faculty member for 37 years prior to his mandatory retirement in 2002. Dr. Abbott is still an active researcher within the Faculty and maintains a small research group. He is currently a member of Health Canada's Expert Advisory Committee on hepatotoxicity. Dr. Abbott recently became the Executive Director of the Association of Faculties of Pharmacy of Canada (AFPC) and the Association of Deans of Pharmacy of Canada (ADPC). He is a founding member of CSPA and has served as treasurer and member at large on the Executive of CSPA. Dr. Abbott's research expertise is in pharmaceutical chemistry with major interests in analytical method development, drug receptor interactions, quantitative structure-activity-relationships, drug metabolism, drug interactions, placental transfer of drugs and toxicological investigations of drugs and metabolites: Publications: Papers and abstracts (160). Book Chapters (4), Presentations (90). He is currently funded by CIHR and the pharmaceutical industry. Dr. Abbott maintains strong connections with the pharmaceutical industry through his former graduate students who now work in the USA and Canada. He was recognized for his research achievements by being awarded the AFPC McNeill Award for excellence in pharmaceutical research.

**Fakhreddin Jamali**

Professor and Associate Dean, Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, Alberta, Canada

Dr. Jamali (Doctor of Pharmacy, University of Tehran, Iran; MSc, pharmaceuticals, PhD, pharmacokinetics, University of British Columbia, Vancouver, Canada) is a professor and the associate dean at the Faculty of Pharmacy and Pharm. Sci., University of Alberta. He joined the faculty at the University of Alberta in 1981. His research interests include effect of pathophysiological changes on the action and disposition of drugs, stereochemical aspects of drugs action and disposition, basic and clinical pharmacology of anti-rheumatic, analgesic and cardiovascular drugs, and toxicology of nonsteroidal antiinflammatory drugs. He has published over 170 refereed articles and has been an invited speaker at many conferences, and has trained over 30 PhDs. He has served as a Theme Leader in the Canadian Arthritis Network (Networks of Centres of Excellence) is a Fellow of American Assoc. Pharm. Sci., and for his research achievements, he has received the McKeen Cattel Memorial Award of the American College of Clin. Pharmacol., the McCalla Professorship of the University of Alberta, the McNeil Award of Assoc Canadian Faculties of Pharm., DuPont Research Leadership Award of the Canadian Soc. Pharm. Sci.. Dr. Jamali has served as a consultant and/or a member of the board of directors of many pharmaceutical houses. He is the founding president of Canadian Soc. Pharm. Sci., editor of J. Pharm. & Pharm. Sci., assoc editor of Eur. J. Med. Chem., and has served in the editorial board of J. Clin. Pharmacol., Chirality and Am. J. Therapeutics and AAPS PharmSci. He teaches pharmacokinetics and is involved in pharmacy curriculum development.



## POSTER PRESENTATIONS

**Molecule to market: biotechnologically-derived  
molecules vs traditional small chemical entities.**

CSPS Posters will be on display in Grand Ballrooms C&D from 8-4 Thursday.

AFPC Posters will be on display in Grand Ballrooms C&D from 8-4 Friday.

*Presenters will be available by their posters during the coffee and lunch breaks.*

### 1 A NOVEL GENOTYPING ALGORITHM FOR THE CYP2D6\*10 ALLELE IN ASIANS USING REAL-TIME RAPID-CYCLE PCR AND MULTIPLEX PCR

*Evan Kwong, Marc Levine, Carolyne J. Montgomery, and Thomas K.H. Chang; Faculty of Pharmaceutical Sciences, University of British Columbia; Department of Anesthesiology, Children's and Women's Health Centre of British Columbia, Vancouver, British Columbia, Canada*

**Purpose.** The CYP2D6\*10 allele is common among Asians and associated with decreased metabolism of some CYP2D6 substrates. To study the effect of this allele on drug metabolism, it is necessary to accurately genotype patients for CYP2D6\*10 (C188T). Based on reported allele frequencies among Asians, it is necessary to rule out CYP2D6\*4 (C188T, G1934A) and CYP2D6\*5 (gene deletion) before inferring the presence of CYP2D6\*1 or CYP2D6\*2 (C188). The project objectives are to devise a genotyping algorithm and to develop and validate genotyping methods for detecting the C188T and G1934A single nucleotide polymorphisms (SNPs) and CYP2D6\*5. **Methods.** Long PCR was used to amplify the CYP2D6 gene. Nested real-time PCR methods to detect the C188T and G1934A SNPs were developed and validated by restriction fragment length polymorphism (RFLP) and sequencing analyses of previously genotyped reference samples (CYP2D6\*1/\*1, CYP2D6\*1/\*4, CYP2D6\*4/\*4). A multiplex PCR method to detect the CYP2D6\*5 allele using published primer sequences was developed and validated using reference samples (CYP2D6\*1/\*1, CYP2D6\*1/\*5, CYP2D6\*5/\*5). **Results.** C188T and G1934A genotyping results using real-time PCR were consistent with RFLP analyses, sequencing analyses, and the genotypes of the reference samples. CYP2D6\*5 genotyping results were also in agreement with the genotypes of the reference samples. **Conclusions.** The combination of real-time PCR to detect the C188T and G1934A SNPs and multiplex PCR to detect CYP2D6\*5 provides an efficient approach for genotyping Asian patients with respect to CYP2D6. The novel genotyping algorithm for the CYP2D6\*10 allele in Asians involves: 1) analysis for the C188T SNP; 2) analysis for the G1934A SNP in those with the C188T SNP; and 3) analysis for CYP2D6\*5 in those who appear homozygous at the 188 locus for C (CYP2D6\*1 or CYP2D6\*2) or T (CYP2D6\*10). This algorithm can be used in future clinical trials to study the effect of the CYP2D6\*10 allele on drug metabolism in Asians.

### 2 THE EFFECT OF VALPROIC ACID ON OXIDATIVE STRESS AND MITOCHONDRIAL FUNCTION IN ISOLATED RAT HEPATOCYTES

*Vincent Tong, Thomas K.H. Chang and Frank S. Abbott; Faculty of Pharmaceutical Sciences, The University of British Columbia, Vancouver, British Columbia, Canada*

Increased production of reactive oxygen species (ROS) has been associated with valproic acid (VPA) treatment and mitochondrial dysfunction has been implicated in the pathogenesis of VPA-idiosyncratic hepatotoxicity. **Objectives.** The present study investigates the effect of VPA on ROS production and mitochondrial function in freshly isolated rat hepatocytes. **Methods.** Hepatocytes were isolated from untreated or phenobarbital-pretreated male Sprague-Dawley rats. Hepatocytes were depleted of glutathione (GSH) by treatment with a combination of L-buthionine sulfoximine (2 mM) and diethylmaleate (0.5 mM). Hepatocyte groups were treated with VPA (0-1000 mg/mL) over a time course of 2 hr and levels of ROS were determined by measuring 8-isoprostane by ELISA and by the oxidative stress fluorescent probe DCFDA. Mitochondrial potential was determined by using the dual-fluorescent dye (JC-1) and cell viability was evaluated by the water-soluble tetrazolium salt WST-1 assay. **Results.** VPA resulted in a time- and dose-dependent increase in ROS markers (8-isoprostane and DCF) and these levels were further elevated in cells with GSH-depletion (2- and 1.5-fold, respectively). The mitochondrial membrane potential was reduced in GSH-depleted hepatocytes at 500 and 1000 mg/mL VPA. Significant cytotoxicity was only observed with the GSH-depleted hepatocytes at 1000 mg/mL VPA ( $p < 0.05$ ). Phenobarbital-pretreated hepatocytes were not different from control over the range of 0-1000 mg/mL VPA with respect to all markers measured. VPA leads to oxidative stress but had no effect on mitochondrial function in rat hepatocytes. The effect on oxidative stress was enhanced by GSH-depletion and this was accompanied by mitochondrial dysfunction. (Supported by CIHR). Presented at the 12<sup>th</sup> North American ISSX Meeting, Providence RI, 2003.

### 3 INVESTIGATING POTENTIAL GLUCOSE LOWERING PROPERTIES OF ORGANIC VANADIUM COMPOUNDS AND TRANSITION ELEMENT-MALTOLATO COMPOUNDS

*Jeremy Tse, Violet G. Yuen, Chris Orvig, and John H. McNeill; Faculty of Pharmaceutical Sciences; and Department of Chemistry, The University of British Columbia, Vancouver, British Columbia, Canada*

**Purpose:** To compare 1) the potential glucose lowering properties between bis (curcumin)-oxovanadium (IV) (BCOV) and bis (ethylmaltolato) oxovanadium (IV) (BEOV) and 2) the acute glucose-lowering response of various maltolato compounds to the known ED<sub>50</sub> for bis (maltolato) oxovanadium (IV) (BMOV). **Methods:** Male rats were made diabetic with a single tail vein injection of streptozotocin 60 mg/kg. All compounds were administered as suspensions by oral gavages. **Cumulative dose response study:** BCOV and BEOV were initially administered at 0.4 mmol/kg and every 24 hours for 1 week. **Chronic study:** BCOV and BEOV were administered for



2 weeks at a dose of 0.2 mmol/kg/day followed by a 3-week period of increasing doses. Blood was collected prior to dosing. *Acute comparison study:* maltolato compounds of vanadium (III), isomaltol, chromium, molybdenum, zinc, cobalt or copper were given as a single dose of 0.6 mmol/kg. Blood was collected prior to drug administration and at 4 through 72 hours subsequently. **Results:** *Cumulative dose response study:* BEOV treatment significantly lowered plasma glucose levels, while BCOV had no effect on plasma glucose. *Chronic study:* 2 weeks of low dose treatment did not affect plasma glucose levels. However, with increasing daily doses, plasma glucose levels were lower in BEOV treated rats only. *Acute comparison study:* only BMOV and the molybdenum compound lowered plasma glucose in four consecutive time points but BMOV alone produced a euglycemic effect. **Conclusions:** BCOV was not an effective glucose-lowering compound under these conditions. Other elemental maltolato compounds did not produce the same glucose lowering response at the ED<sub>50</sub> dose for BMOV. These data suggest that vanadium is superior amongst transition elements for glucose lowering properties. **Acknowledgements:** Funding provided by the Merck Company Foundation National Summer Student Research Program 2003 and a grant from CIHR.

#### 4 CACO-2 CELLULAR ACCUMULATION AND TRANSEPIHELIAL FLUX OF P-GLYCOPROTEIN SUBSTRATES WITH METHOXYPOLYETHYLENE GLYCOL-BLOCK-POLYCAPROLACTONE AMPHIPHILIC DIBLOCK COPOLYMERS: DEPENDENCE ON P-GLYCOPROTEIN SUBSTRATE HYDROPHOBICITY

Jason Zastre, John Jackson, and Helen M. Burt; Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, British Columbia, Canada

**Purpose:** To compare the caco-2 cellular accumulation and transepithelial flux of P-glycoprotein substrates with different hydrophobicities using methoxypolyethylene glycol-block-polycaprolactone (MePEG-b-PCL) amphiphilic diblock copolymers. **Methods:** Cellular accumulation and transepithelial flux of the P-glycoprotein substrates, rhodamine 123 (R-123), rhodamine 6G (R-6G), paclitaxel, and doxorubicin, which differ in their relative hydrophobicity were studied. For cellular accumulation studies, caco-2 cells were incubated for 90 min at 37°C with 5.0 μM R-123, 0.25 μM R-6G, 10 μM doxorubicin, or 0.5 μM paclitaxel with or without diblock composed of MePEG with 17 repeat units of ethylene glycol and 5 repeat units of polycaprolactone (denoted as MePEG<sub>17</sub>-b-PCL<sub>5</sub>). Directional flux in the apical to basolateral (AP→BL) or BL→AP direction was determined over 120 min at 37°C using caco-2 monolayers grown on Transwell® membranes. **Results:** For all four P-glycoprotein substrates, as the concentration of MePEG<sub>17</sub>-b-PCL<sub>5</sub> increased, the accumulation increased up to

a critical diblock concentration, after which accumulation began to decrease. Accumulation enhancement of R-123 was 3.8 fold with 0.25% MePEG<sub>17</sub>-b-PCL<sub>5</sub>, however R-6G accumulation increased 2.8 fold at 0.01% MePEG<sub>17</sub>-b-PCL<sub>5</sub>. Moreover, the accumulation for R-6G was enhanced approximately two fold at concentrations as low as 0.0001% MePEG<sub>17</sub>-b-PCL<sub>5</sub>. Similarly, the hydrophilic doxorubicin required a high concentration of 1.0% MePEG<sub>17</sub>-b-PCL<sub>5</sub> to enhance accumulation 1.8 fold compared to the hydrophobic paclitaxel which demonstrated a similar accumulation profile to the hydrophobic R-6G. MePEG<sub>17</sub>-b-PCL<sub>5</sub> or verapamil demonstrated no increase in R-123 AP→BL flux. However, both were able to significantly enhance the AP→BL flux for R-6G. Furthermore, MePEG<sub>17</sub>-b-PCL<sub>5</sub> and verapamil were able to significantly reduce the BL→AP flux of R-123 and R-6G. **Conclusion:** Differences in MePEG<sub>17</sub>-b-PCL<sub>5</sub> diblock concentration required to enhance cellular accumulation and the difference in AP→BL flux enhancement of P-glycoprotein substrates with different relative hydrophobicities suggests that a membrane permeability enhancement effect maybe involved in addition to a reduction of P-glycoprotein mediated efflux.

#### 5 EFFECT OF HEAT TREATMENT ON THE AMPHOTERICIN B-INDUCED CYTOTOXICITY OF LLC PK1 RENAL CELLS AND CRYPTOCOCCUS NEOFORMANS

Karen Bartlett and Kishor Wasan; School of Occupational and Environmental Hygiene; Division of Clinical Pharmacy and Division of Pharmaceutics and Biopharmaceutics, Faculty of Pharmaceutical Sciences, The University of British Columbia, Vancouver, British Columbia, Canada

**Purpose:** The purpose of this investigation was to determine the cytotoxicity of amphotericin B (AmpB) following administration of AmpB lipid complex (ABLC), Fungizone<sup>®</sup> (FZ) and a heat-treated form of FZ (HFZ) to LLC PK<sub>1</sub> pig kidney cells and *Cryptococcus neoformans* var. *gattii* from various sources. **Methods:** Fungizone<sup>®</sup> (FZ) was heated at 70°C for 20 minutes to produce heat-treated Fungizone<sup>®</sup> (HFZ). LLC PK<sub>1</sub> renal cells were incubated for 18 h at 37°C in serum-containing medium that contained either no treatment (controls), ABLC, FZ or HFZ at 10, 20 and 50 mg AmpB / ml (n=6). Percent renal cytotoxicity versus control was determined using an MTS assay. In addition, the concentration required to inhibit 50% of fungal cell growth of various cryptococcal strains compared to controls (MIC<sub>50</sub>) of ABLC, FZ and HFZ (n=6) was determined. **Results:** For the renal cell studies, HFZ was significantly less toxic (non-detectable to 44.4+/-5.7% toxicity versus control) than FZ (18.5+/-17.9 to 76.5+/-9.1% toxicity versus control) for all concentrations tested. ABLC was found to be the least toxic for all concentrations tested. For the fungal cell studies, the concentration range which resulted in a 50% reduction of

growth ( $MIC_{50}$ ) for both FZ and HFZ was 0.125 – 1 mg/mL (mode =1); for ABLC the range was 0.25 – 0.03 mg/mL (mode =0.125) ( $p < 0.01$ ). **Conclusions:** These findings suggest that renal cytotoxicity is decreased without modifying the antifungal activity of AmpB when FZ is subjected to heat treatment.

**Acknowledgements:** This work was supported with a grant from the Canadian Institutes of Health Research (Grant #MOP-14484 to KM Wasan). The study was supported in part by the Michael Smith Foundation for Health Research (K.H. Bartlett, Scholar).

#### 6 EFFECT OF VARIOUS LIPID-BASED ORAL FORMULATIONS ON PLASMA AND TISSUE CONCENTRATIONS AND RENAL TOXICITY OF AMPHOTERICIN B WITHIN MALE RATS

Verica Risovic, Michael Boyd, Eugene Choo and *Kishor Wasan*<sup>†</sup> Division of Pharmaceutics and Biopharmaceutics, Faculty of Pharmaceutical Sciences; Acute Care Animal Unit, Koerner Pavilion, University of British Columbia, Canada

**Purpose:** The purpose of this study was to determine the effect of various lipid and mixed micelle formulations on the oral absorption and renal toxicity of amphotericin B (AmpB) within the rat. **Methods:** Rats were divided into six treatment groups and received a single oral gavages of either: AmpB solubilized in methanol (1, 5 and 50 mg AmpB/kg), Fungizone (DOC-AmpB; 1, 5, and 50 mg AmpB/kg), amphotericin B lipid complex (ABLC 50 mg AmpB/kg), AmpB incorporated into 10% Intralipid (50 mg AmpB/kg), or AmpB incorporated into 100% Peceol (5 and 50 mg AmpB/kg). Blood samples (0.5 ml) were obtained prior to and 2.0, 4.0, 8.0, 10 and 24 hr post-oral gavages. Plasma was immediately harvested by centrifugation and analyzed for drug by HPLC. Following the last blood draw, each rat was humanely sacrificed and the liver, right kidney spleen, heart and lung were removed, dried, and weighed. **Results:** Plasma AmpB  $C_{max}$  and  $AUC_{[0-24h]}$  were elevated in rats administered triglyceride (TG)-rich AmpB formulations (e.g. Intralipid-AmpB;  $C_{max} = 769 \pm 213$  ug/ml & Peceol-AmpB;  $C_{max} = 1469 \pm 891$  ug/ml at 50 mg/kg dose) compared to DOC-AmpB ( $C_{max} = 39.8 \pm 22$  ug/ml), ABLC ( $C_{max} = 48.5 \pm 25$  ug/ml) or AmpB solubilized in methanol ( $C_{max}$  = non-detectable AmpB levels) at 50 mg/kg dose. Furthermore, our findings suggest that AmpB incorporated into TG-based oral formulations (e.g. Intralipid & Peceol) are less renal toxic than intravenous or orally administered DOC-AmpB by decreasing the concentration of AmpB recovered in the kidney and increasing the concentration of AmpB recovered in the liver. **Conclusions:** In conclusion, we have demonstrated significant differences in the plasma concentration, tissue distribution and drug-induced renal toxicity of AmpB following the administration of TG-rich oral formulations of AmpB compared to intravenous and oral DOC-AmpB and that altering

the tissue distribution of AmpB can modify its AmpB-induced renal toxicity. **Acknowledgements:** This study was supported with an Operating Grant from the Canadian Institutes of Health Research (Grant #MOP-449432 to KMW).

#### 7 A COMPARISON OF PURE MATRINE AND CRUDE MATRINE TRANSPORT ACROSS THE CACO-2 CELLS MONOLAYER

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**Objectives.** The purpose of the current investigation was to compare the transport of pure matrine with those of crude matrine in an Acapha<sup>®</sup> extract using the Caco-2 cells monolayer. **Methods.** Acapha<sup>®</sup> was extracted by 70% ethanol. The chemical profile of the ethanolic extract was determined using high performance liquid chromatography (HPLC). The amount of matrine in the extract was determined using a selected ion monitoring gas chromatography/mass spectrometry (SIM/GC/MS) method developed in our laboratory. Caco-2 cells were seeded as a monolayer of  $0.5 \times 10^6$  cells in the inserts of a 12-well plate. Pure matrine or Acapha<sup>®</sup> extract was applied from either the apical or the basolateral side of the Caco-2 cells monolayer. At pre-determined time point, an aliquot of Dulbecco's Modified Eagle's medium (DMEM) was taken from the opposite chamber compartment and replaced by an equal volume of fresh DMEM. The amount of permeated matrine in the DMEM samples was determined by SIM/GC/MS. **Results.** At least six major peaks were identified in the HPLC chromatogram of the Acapha<sup>®</sup> extract. However, only matrine and two unknown chemicals in the extract were able to cross the Caco-2 cells monolayer. The influence of incubation time on the flux of matrine across the Caco-2 cells monolayer was examined using various pure matrine and crude matrine concentrations. Matrine flux was linear with time for ~0.5 h in both directions of the Caco-2 cells monolayer. The effective permeability ( $P_{eff}$ ) (cm/sec) was determined using equation:  $P_{eff} = dC/dt * V_r / A C_o$  where  $dC/dt$  is the flux determined by the linear slope of receptor drug concentration versus time plot after correcting for dilution,  $V_r$  is the volume of the receptor chamber,  $A$  is the surface area of the filter ( $0.9 \text{ cm}^2$ ),  $C_o$  is the initial drug concentration.  $P_{eff}$  for pure matrine in apical to basolateral transport was much higher than that of crude matrine in the Acapha<sup>®</sup> extract. The  $P_{eff}$  of pure matrine was similar to that of crude matrine in basolateral to apical transport. **Conclusion.** Only a few phytochemicals in the Acapha<sup>®</sup> extract were able to cross the Caco-2 cells monolayer. The smaller  $P_{eff}$  of crude matrine in apical to basolateral transport might be due to binding with Acapha<sup>®</sup> matrices, decreasing delivery and/or uptake of crude matrine by the Caco-2 cells (Supported by NIH grant no.1 U01 CA96109-01).

## 8 A RECONFIGURABLE AMPLIFIER PERMITTING A HIGH DYNAMIC RANGE FOR X-RAY MEDICAL IMAGING

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**Purpose** Digital imagers using amorphous silicon (a-Si:H) are increasingly being used for large area medical imaging. In diagnostic X-ray imaging, a-Si:H digital imagers allow the benefit of telediagnosis. In real-time digital fluoroscopy, the patient is continuously exposed to radiation requiring low doses, hence reducing the input signal to the digital imaging pixel electronics. Industry standard a-Si pixels results in blurred images at low fluoroscopic exposure levels. Current-mediated a-Si pixel amplifiers have been reported to give a good SNR for fluoroscopy with low X-ray doses. However, their output becomes non-linear at higher dosages, thus reducing the pixel dynamic range and making it impractical for fluoroscopy. In this research, a custom charge amplifier with preprocessing circuitry capable of extending the dynamic range of a-Si:H pixel amplifiers to perform real-time fluoroscopy, and higher contrast chest radiography, is discussed. **Methods** A reconfigurable custom charge amplifier capable of extending the dynamic range of a-Si pixel amplifiers was designed to perform both, real-time fluoroscopy and higher contrast chest radiography. The low noise amplifier was simulated under realistic APS TFT operations. **Results** Results confirm that small signal linearity of the system is achievable with the custom readout circuitry for realistic current-mediated APS operations. The LNA is able to improve the dynamic range of the C-APS, while allowing a good SNR ratio at low exposure fluoroscopic application. The readout circuitry can be reconfigured in order to extend the dynamic range of the APS, and obtain a radiographic image of a region of interest. The reconfigured LNA serves permits the ability to capture higher exposure input signals. **Conclusion** The custom column readout circuitry has the ability to extend the dynamic range of a-Si current mediated pixel amplifiers. The LNA can increase the range of an a-Si digital imaging array, compensating for non-linear outputs observed at high dosages.

## 9 HIGH DYNAMIC RANGE PIXEL ARCHITECTURES FOR DIAGNOSTIC MEDICAL IMAGING

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**Purpose** One approach to increase pixel signal-to-noise ratio (SNR) in low exposure, digital fluoroscopy is to employ in-situ pixel amplification via a current-mediated active pixel sensor (C-APS). A challenge with the C-APS circuit exists where larger input voltages cause the C-APS output to be non-linear thus reducing the pixel dynamic range. In this research, we investi-

gate amplified pixel architectures that exhibit large signal linearity and higher dynamic range. **Methods** Our proposed high dynamic range pixel architectures have the potential to enable a large area, active matrix flat panel imager (AMFPI) to switch instantly between low exposures, fluoroscopic imaging and higher exposure radiographic imaging modes. The high dynamic range pixel circuits are based on amplified pixels and suitable for integration with on-panel multiplexers for both gate and data lines, which can further reduce off-panel circuit complexity. **Results** The results of our proposed hybrid active pixel sensor (H-APS) architecture is capable of providing both, a charge gain for improved SNR and large signal linearity with unity gain for larger sensor inputs. The H-APS has one additional thin film transistor in contrast to the C-APS, which slightly degrades gain and noise performance. However, simulation results indicate that the impact of the additional TFT can be minimized if state-of-the-art scaled down; vertically stacked a-Si TFT processes are used. **Conclusion** The high dynamic range, amplified pixel circuits presented in this paper are of particular relevance to the development of advanced X-ray imagers that can switch instantly between low exposure, fluoroscopic imaging and higher exposure radiographic imaging modes.

## 10 DETERMINATION OF MATRINE IN HUMAN PLASMA USING SELECTIVE ION MONITORING GAS CHROMATOGRAPHY MASS SPECTROMETRY

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**Objectives:** Matrine is a major alkaloid of the *S. flavescens* roots. Previous pharmacokinetic studies have used HPLC/UV to determine matrine concentrations in blood or tissue samples. However, the HPLC/UV is unlikely to detect any matrine in the plasma of humans after receiving an oral dose of the Sophora roots because of low method sensitivity. The objective of the present work was to develop and validate a sensitive GC/MS method for determining matrine in plasma samples. **Methods:** 12, 12-D<sub>2</sub>-Matrine was prepared from unlabeled matrine by deuterium exchange and used as an internal standard of the analysis. Calibration standards (10, 15, 25, 50, 100, 250, 500 ng/ml) were prepared by mixing various amounts of unlabeled matrine with 250ng of deuterated matrine in 1 ml human plasma. Matrine was extracted into 200 ml toluene:butanol (v/v 9:1), which was analyzed by GC/MS. The molecular ions *m/z* 248 and *m/z* 250 were used to monitor matrine and deuterated matrine, respectively. **Results:** Linear detection responses were observed for matrine concentrations ranging from 10 – 500 ng/ml. The intra-day precision ranged from 0.4 – 11.8% and inter-day precision ranged from 5 – 8.3%. The intra-day accuracy was between – 7.32 – 15.2percent. The limit of quantification was 10 ng/ml.

**Conclusions:** A method was developed and validated for quantifying matrine in human plasma using a liquid-liquid extraction procedure followed by GC/MS analysis. The GC/MS method is currently used to quantify matrine in the plasma samples of a clinical pharmacokinetic study. This poster was presented in the First Natural Health Product Research Conference held in Montreal, Quebec during February 20-22, 2004.

#### 11 METABOLISM OF 20-(S)-PROTOPANAXDIOL (PPD) AND 20-(S)-PROTOPANAXTRIOL (PPT) BY HUMAN LIVER MICROSOMES IN VITRO

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**Objectives:** Previous ginseng biotransformation studies have focused mainly on the hydrolysis or deglycosylation of ginsenosides by the gastrointestinal tract and/or enteric bacteria. Very little is known of the biotransformation of ginsenoside aglycons by the liver. The objectives of the present study were to examine the *in vitro* metabolism of PPD and PPT by human liver microsomes and to determine their  $K_m$  and  $V_{max}$  values. **Methods:** The incubation mixture consisted of an NADPH-generating system, human liver microsomes (0.3 mg/ml protein), potassium phosphate buffer (0.1M, pH 7.4) and various PPD (or PPT) concentrations in 10% mulgofen suspension. After a 10-min incubation, the reaction was stopped by the addition of cold acetone. The mixture was extracted by 2 ml of hexane containing 9 mg of the internal standard, dihydrocholesterol. The hexane layer was removed and dried under a gentle stream of  $N_2$ . The remaining residues were derivatized with a mixture of BSTFA:TMSI:TMSCI (3:3:2). The PPD and PPT derivatives were quantified by GC/MS; the ions  $m/z$  199 was used to monitor PPD and PPT; the ion  $m/z$  215 was used to monitor dihydrocholesterol. PPD and PPT metabolism rates were calculated based on the disappearance of PPD and PPT from the incubation mixture. **Results:** No PPD and PPT metabolism occurred if the NADPH-generating system or human liver microsomes were omitted in the incubation. The  $K_m$  and  $V_{max}$  of PPD metabolism were 93.3 mM and 0.565 nmol/mg protein/min respectively. Based on HPLC/MS analysis, PPD was metabolized by human liver microsomes to a single, hydroxylated metabolite. Similar results were observed in the PPT metabolism studies. **Conclusions:** *In vitro* PPD and PPT metabolism were mediated by the human liver mixed-function oxidase system.

#### 12 A SELECTIVE AND SENSITIVE LIQUID CHROMATOGRAPHY MASS SPECTROMETRY METHOD FOR THE DETERMINATION OF

BENAZEPRIL, BENAZEPRILAT AND HYDROCHLOROTHIAZIDE IN HUMAN PLASMA  
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**Purpose** To develop and validate an LC/MS method for the quantitative determination of benazepril, benazeprilat and hydrochlorothiazide in human plasma. Benazepril hydrochloride in combination with hydrochlorothiazide is used in the treatment of hypertension. **Methods** Benazepril, benazeprilat, and their internal standard quinaprilat, and hydrochlorothiazide and its internal standard trichlormethiazide were extracted from human plasma by solid phase extraction from 1 mL plasma using Waters Oasis<sup>®</sup> HLB 3cc 60 mg cartridge and methanol as eluent. The analytes were chromatographically separated on an Agilent Extend-C18 (4.6'50 mm, 3.5 mm) column using gradient elution followed by LC-ESI-MS analysis. Quantitation was carried out by monitoring selected ions at  $m/z$  425.2 (benazepril),  $m/z$  397.1 (benazeprilat),  $m/z$  411.1 (quinaprilat),  $m/z$  296.0 (hydrochlorothiazide) and  $m/z$  380.0 (trichlormethiazide). **Results** The method was validated over a concentration range from 2.00 to 750 ng/mL (benazepril), 4.00 to 750 ng/mL (benazeprilat) and 5.00 to 500 ng/mL (hydrochlorothiazide), with correlation coefficients of  $0.9995 \pm 0.0002$ ,  $0.9990 \pm 0.0003$ , and  $0.9969 \pm 0.0015$ , respectively. The calibration standard samples inter-batch precision (%CV) ranged from 2.1 to 4.5 for benazepril, from 1.9 to 3.8 for benazeprilat and from 6.3 to 10.8 for hydrochlorothiazide. The inter-batch accuracy (%RE) ranged from -3.9 to 2.6 for benazepril, -5.3 to 3.1 for benazeprilat and from -3.4 to 4.4 for hydrochlorothiazide. The inter-batch assay precision (%CV) for quality control samples ranged from 1.6 to 2.7 for benazepril, from 0.9 to 1.6 for benazeprilat and from 2.1 to 6.6 for hydrochlorothiazide with assay accuracy (%RE) ranging from -8.7 to -1.0 for benazepril, -8.1 to -0.3 for benazeprilat and from -7.1 to 2.9 for hydrochlorothiazide. The mean assay recovery was  $85.3 \pm 2.4\%$ ,  $87.1 \pm 5.5\%$  and  $78.3 \pm 4.4\%$  for benazepril, benazeprilat and hydrochlorothiazide, respectively. **Conclusions** A sensitive, reproducible and selective analytical assay was developed, validated and used to quantify over four thousand plasma samples to support a bioequivalence study. Abstract presented at the American Association of Pharmaceutical Scientists Annual Meeting (Salt Lake City, Utah, Oct. 26 -30, 2003)

#### 13 DEVELOPMENT AND VALIDATION OF A LIQUID CHROMATOGRAPHY MASS SPECTROMETRY ASSAY METHOD FOR THE DETERMINATION OF FEXOFENADINE IN HUMAN PLASMA

*Luis Sojo, Adrien Musuku, Gina Lum, Priscilla Chee, Sandra Jungwirth, Nancy Eng, and James E. Axelson; Axelson BioPharma Research, Burnaby; Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, British Columbia, Canada*

**Purpose** Fluticasone propionate ((6a,11b,16a,17a)-6,9-Difluoro-11-hydroxy-16-methyl-3-oxo-17-(1-oxopropoxy)androst-1,4-diene-17-carbothioic acid S-(fluoromethyl) ester) is a synthetic corticosteroid with a potent anti-inflammatory activity used in the treatment of chronic inflammatory airway disorders such as seasonal allergic rhinitis and steroid-responsive bronchial asthma. The purpose of this work was to develop and validate a sensitive electrospray positive ion LC-MS/MS assay method for the measurement of fluticasone propionate in human plasma at low pg/mL levels. **Methods** Fluticasone propionate and the internal standard (11-b-acetoxy fluticasone propionate) were extracted from 1.00 mL human plasma samples by liquid-liquid extraction using n-butyl chloride. Fluticasone and its internal standard were chromatographed on a reverse-phase ACE 3 AQ C<sub>18</sub> (50 × 4.6 ID mm, 3.5 mm) column using gradient elution followed by ESI-MS/MS detection. Quantitation was carried out by monitoring the transitions m/z 501.1 → m/z 313.2 (fluticasone propionate) and m/z 543.3 → m/z 293.1 (11-b-acetoxy fluticasone propionate). **Results** The method was validated over a concentration range from 3.00 to 100 pg/mL using a linear calibration curve with a weighing factor of 1/x. The calibration standard samples inter-batch precision (%CV) ranged from 3.1 to 16.9. The inter-batch accuracy (%RE) ranged from -4.1 to 4.4, indicating an acceptable goodness-of-fit. The inter-batch assay precision (%CV) for quality control samples ranged from 1.1 to 6.3 over four concentration levels. The inter-batch assay accuracy (%RE) results for quality control samples ranged from -3.7 to 1.3 over four concentration levels. The mean assay recovery for fluticasone propionate was 82.6 ± 8.1%. Freeze and thaw stability was established at -40°C and -70°C for 3 cycles at each temperature. The analytical method was subsequently used to support a pilot bioequivalence study. **Conclusions** A sensitive, accurate and selective method for the quantitative determination of fluticasone propionate in human plasma was developed and validated over the concentration range from 3.00 pg/mL to 100 pg/mL. Abstract presented at the American Association of Pharmaceutical Scientists Annual Meeting (Salt Lake City, Utah, Oct. 26 –30, 2003)

#### 14 DEVELOPMENT AND VALIDATION OF A LIQUID CHROMATOGRAPHY MASS SPECTROMETRY ASSAY METHOD FOR THE DETERMINATION OF LEFLUNOMIDE AND LEFLUNOMIDE METABOLITE (A77 1726) IN HUMAN PLASMA

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*Gina Lum, Nancy Eng, and James E. Axelson; Axelson BioPharma Research, Burnaby; Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, British Columbia, Canada*

**Purpose** To develop and validate an LC/MS method for the measurement of leflunomide, used in the treatment of rheumatoid arthritis, and its active metabolite (A77 1726) in human plasma. **Methods** Leflunomide, A77 1726 and their respective internal standards were extracted from 0.5 mL human plasma by liquid/liquid extraction using 6 mL chlorobutane. The analytes were separated on an Agilent Extend-C<sub>18</sub> (4.6 × 50 mm, 3.5 mm) column for leflunomide and Agilent Zorbax Extend C<sub>18</sub> (4.6 × 50 mm, 3.5 mm) column for A77 1726) using 10 mM AqNH<sub>4</sub>OAc/CH<sub>3</sub>CN:60/40 (v/v) for leflunomide and 0.01% CH<sub>3</sub>COOH in 1 mM AqNH<sub>4</sub>OAc/CH<sub>3</sub>CN:51/49 (v/v) for A77 1726. Detection was carried out with an Agilent 1100 series LC/MS by monitoring selected ions in ESI negative mode at m/z 269.0 (leflunomide), m/z 273.0 (4C<sup>13</sup>-leflunomide, IS for leflunomide), m/z 269.0 (A77 1726) and m/z 273.0 (4C<sup>13</sup>-A77 1726, IS for A77 1726). **Results**. The calibration standard samples inter-batch precision (%CV) for leflunomide ranged from 1.6 to 3.8 and the accuracy (%RE) ranged from -6.4 to 5.2 over a linear range of 0.20 to 12.00 ng/mL. Similarly, the inter-batch precision (%CV) for A77 1726 ranged from 1.2 to 3.1, and the accuracy (%RE) ranged from -7.8 to 3.7 over a linear range of 100.00 to 12000 ng/mL. The inter-batch assay precision (%CV) for quality control samples ranged from 0.7 to 3.2 with an inter-batch accuracy (%RE) ranging from 0.8 to 5.7 for leflunomide. The inter-batch precision (%CV) ranged from 0.6 to 3.8 with an inter-batch accuracy (%RE) ranging from 0.3 to 6.5 for A77 1726. The mean correlation coefficients were 0.9987 ± 0.0009 (leflunomide) and 0.9987 ± 0.0004 (A77 1726). The mean assay recovery was 85.0 ± 1.9% (leflunomide) and 88.4 ± 1.7% (A77 1726). **Conclusions** An accurate and sensitive analytical assay was developed and successfully applied for the measurement of leflunomide and A77 1726 in human plasma samples. Abstract presented at the American Association of Pharmaceutical Scientists Annual Meeting (Salt Lake City, Utah, Oct. 26 –30, 2003)

#### 15 DEVELOPMENT AND VALIDATION OF A LIQUID CHROMATOGRAPHY MASS SPECTROMETRY ASSAY METHOD FOR THE DETERMINATION OF MODAFINIL IN HUMAN PLASMA

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**Purpose.** To develop and validate a sensitive electrospray negative ion LC/MS method for the measurement of modafinil, a wakefulness-promoting agent, in human plasma. **Methods** Modafinil and the internal standard (trichlormethiazide) were extracted from 0.25 mL human plasma by liquid/liquid extraction using methyl t-butyl ether as extraction solvent. The analytes were chromatographically separated on a reverse-phase Agilent Eclipse XDB-C<sub>18</sub> (4.6'50 mm, 3.5 mm) column at a flow rate of 0.4 mL/min with an analysis time of 3.5 minutes, followed by ESI-MS detection. Compounds were eluted using a mobile phase of 10 mM aqueous ammonium acetate/acetonitrile: 50/50 (v/v). Quantitation was carried out with an Agilent 1100 Series LC/MS by monitoring selected ions at m/z 272.0 (modafinil) and at m/z 380.0 (trichlormethiazide). **Results** The method was validated over a concentration range from 0.10 to 15.00 mg/mL using a linear calibration curve with a weighing factor of 1/x<sup>2</sup>. No matrix interference was observed at the retention time of the analytes, indicating the specificity of the method. The calibration standard samples inter-batch precision (%CV) ranged from 2.8 to 5.8. The inter-batch accuracy (%RE) ranged from -0.9 to 1.7, indicating an acceptable goodness-of-fit. The inter-batch assay precision (%CV) for quality control samples, based on the individual batch means, ranged from 2.9 to 6.7. The inter-batch assay accuracy (%RE) results for quality control samples ranged from -2.0 to 3.2. The assay recovery for modafinil was 78.5±2.3% (%CV of 2.9, n=5), and 78.3±2.6% (%CV of 3.3, n=5) at 0.25 mg/mL and 14.00 mg/mL, respectively. Freeze and thaw stability was established at -40°C and -70°C for 3 cycles at each temperature. **Conclusions** An accurate, robust, specific, sensitive and rapid analytical assay was developed and validated for the measurement of modafinil in human plasma samples. *Abstract presented at the American Association of Pharmaceutical Scientists Annual Meeting (Salt Lake City, Utah, Oct. 26 -30, 2003)*

#### 16 DEVELOPMENT AND VALIDATION OF A LIQUID CHROMATOGRAPHY MASS SPECTROMETRY ASSAY METHOD FOR THE DETERMINATION OF BENAZEPRIL AND BENAZEPRILAT IN HUMAN PLASMA

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**Purpose** To develop and validate an LC/MS method for the simultaneous determination of benazepril and benazeprilat in human plasma. Benazepril is an angiotensin-converting enzyme inhibitor used as a prodrug in the treatment of hypertension. It is de-esterified in vivo to the pharmacologically more active metabolite, benazeprilat. **Methods** Benazepril, benazeprilat and the internal standard quinaprilat were extracted from human

plasma by solid phase extraction from 0.5 mL plasma using Waters Oasis<sup>®</sup> HLB 3cc 60 mg extraction cartridges and methanol as eluent. The analytes were chromatographically separated on an Agilent Extend-C18 (4.6'50 ID mm, 3.5 mm) column using gradient elution with 0.01%TFA in H<sub>2</sub>O and 0.01%TFA in MeOH as mobile phase followed by LCESI-MS analysis. Quantitation was carried out by monitoring selected ions at m/z 425.2 (benazepril), m/z 397.1 (benazeprilat) and at m/z 411.1 (quinaprilat). **Results** The method was validated over a concentration range from 2.00 to 1000 ng/mL for benazepril and 4.00 to 1000 ng/mL for benazeprilat. No matrix interference was observed at the retention times of the analytes. The calibration standard samples inter-batch precision (%CV) ranged from 3.0 to 10.0 for benazepril and from 3.3 to 6.6 for benazeprilat. The inter-batch accuracy (%RE) ranged from -2.9 to 2.8 for benazepril and -3.9 to 5.6 for benazeprilat. The inter-batch assay precision (%CV) for quality control samples ranged from 2.9 to 7.1 for benazepril and from 0.9 to 8.2 for benazeprilat. The inter-batch assay accuracy (%RE) results for quality control samples ranged from -2.7 to 2.3 for benazepril and -2.2 to 6.8 for benazeprilat. The mean correlation coefficients were 0.9996±0.0002 (benazepril) and 0.9971±0.0008 (benazeprilat). The mean assay recovery was 104.4±3.3% (benazepril) and 100.3±2.9% (benazeprilat). **Conclusions** An accurate, sensitive and rapid analytical assay was developed and successfully applied for the measurement of benazepril and benazeprilat in clinical human plasma samples. *Abstract presented at the American Association of Pharmaceutical Scientists Annual Meeting (Salt Lake City, Utah, Oct. 26 -30, 2003)*

#### 17 DEVELOPMENT AND VALIDATION OF A LIQUID CHROMATOGRAPHY TANDEM MASS SPECTROMETRY ASSAY METHOD FOR THE DETERMINATION OF FLUTICASONE PROPIONATE IN HUMAN PLASMA

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**Purpose** Fluticasone propionate ((6a,11b,16a,17a)-6,9-Difluoro-11-hydroxy-16-methyl-3-oxo-17-(1-oxopropoxy)androsta-1,4-diene-17-carbothioic acid S-(fluoromethyl) ester) is a synthetic corticosteroid with a potent anti-inflammatory activity used in the treatment of chronic inflammatory airway disorders such as seasonal allergic rhinitis and steroid-responsive bronchial asthma. The purpose of this work was to develop and validate a sensitive electrospray positive ion LC-MS/MS assay method for the measurement of fluticasone propionate in human plasma at low pg/mL levels. **Methods** Fluticasone propionate and the internal standard (11-b-acetoxy fluticasone propionate) were extracted from 1.00 mL

human plasma samples by liquid-liquid extraction using n-butyl chloride. Fluticasone and its internal standard were chromatographed on a reverse-phase ACE 3 AQ C<sub>18</sub> (50 × 4.6 ID mm, 3.5 mm) column using gradient elution followed by ESI-MS/MS detection. Quantitation was carried out by monitoring the transitions m/z 501.1 → m/z 313.2 (fluticasone propionate) and m/z 543.3 → m/z 293.1 (11-b-acetoxy fluticasone propionate). **Results** The method was validated over a concentration range from 3.00 to 100 pg/mL using a linear calibration curve with a weighing factor of 1/x. The calibration standard samples inter-batch precision (%CV) ranged from 3.1 to 16.9. The inter-batch accuracy (%RE) ranged from -4.1 to 4.4, indicating an acceptable goodness-of-fit. The inter-batch assay precision (%CV) for quality control samples ranged from 1.1 to 6.3 over four concentration levels. The inter-batch assay accuracy (%RE) results for quality control samples ranged from -3.7 to 1.3 over four concentration levels. The mean assay recovery for fluticasone propionate was 82.6 ± 8.1%. Freeze and thaw stability was established at -40°C and -70°C for 3 cycles at each temperature. The analytical method was subsequently used to support a pilot bioequivalence study. **Conclusions** A sensitive, accurate and selective method for the quantitative determination of fluticasone propionate in human plasma was developed and validated over the concentration range from 3.00 pg/mL to 100 pg/mL. Abstract presented at the American Association of Pharmaceutical Scientists Annual Meeting (Salt Lake City, Utah, Oct. 26–30, 2003)

#### 18 DEVELOPMENT AND VALIDATION OF A LIQUID CHROMATOGRAPHY MASS SPECTROMETRY ASSAY METHOD FOR THE DETERMINATION OF FEXOFENADINE AND PSEUDOEPHEDRINE IN HUMAN PLASMA

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**Purpose** Fexofenadine is an antihistamine and the major active metabolite of terfenadine. Pseudoephedrine is a sympathomimetic used as a decongestant. The purpose of this work was to develop and validate an electrospray positive ion LC/MS method for the simultaneous measurement of fexofenadine and pseudoephedrine in human plasma. **Methods** Fexofenadine, pseudoephedrine and their respective internal standards were extracted from human plasma by solid phase extraction from 0.5 mL plasma using Waters Oasis HLB 3 cc 60 mg Solid Phase Extraction (SPE) Cartridges. The analytes were chromatographically separated on a reverse-phase Agilent Zorbax Eclipse-C18 (4.6 × 50 mm, 3.5 μm) column using gradient elution followed by ESI-MS detection. Quantitation was carried out by monitoring selected ions at m/z 502.1 (fexofenadine),

m/z 508.1 (fexofenadine-d<sub>6</sub>, IS for fexofenadine), m/z 148.1 (pseudoephedrine) and m/z 151.2 (ephedrine-d<sub>3</sub>, IS for pseudoephedrine). **Results** The method was validated over a concentration range from 1.00 to 400 ng/mL using a linear calibration curve (weight 1/x<sup>2</sup>) for fexofenadine and from 2.00 to 400 ng/mL using a linear calibration curve (weight 1/x<sup>2</sup>) for pseudoephedrine. The calibration standard samples inter-batch precision (%CV) for fexofenadine ranged from 0.8 to 5.3. The accuracy (%RE) ranged from -3.5 to 1.7, indicating an acceptable goodness-of-fit. Similarly, the inter-batch precision (%CV) for pseudoephedrine ranged from 1.2 to 4.7, with accuracy (%RE) ranging from -2.2 to 1.0. The inter-batch assay precision (%CV) for quality control samples ranged from 0.1 to 6.6 with accuracy (%RE) from 0.5 to 7.3 for fexofenadine. The inter-batch assay precision (%CV) for quality control samples ranged from 1.8 to 5.2 with accuracy (%RE) from -4.3 to 1.3 for pseudoephedrine. The mean assay recovery was 88.6 ± 2.9%, and 76.3 ± 6.9% for fexofenadine and pseudoephedrine, respectively. **Conclusions** An accurate and sensitive analytical assay was developed for the measurement of fexofenadine and pseudoephedrine in human plasma samples. Abstract presented at the American Association of Pharmaceutical Scientists Annual Meeting (Salt Lake City, Utah, Oct. 26–30, 2003)

#### 19 ADJUVANT TREATMENT WITH GLYCO-PROTEIN IIB/IIIA ANTAGONIST REDUCES PERFUSION DEFICITS AND IMPROVES CEREBRAL BLOOD CIRCULATION AFTER MIDDLE CEREBRAL ARTERY OCCLUSION, IN RAT MODEL OF EMBOLIC STROKE

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**Background and Purpose:** Platelets play a variety of functions in the blood circulation. Their major role is participating in haemostatic mechanisms to synthesize fatty acids and phospholipids leading to platelet activation and aggregation followed by fibrin deposition, which are the most considerable components of microvascular thrombosis and are involved in progressive impairment of downstream microvasculature. It has been hypothesized that inhibition of platelet function with glyco-protein (GP) IIB/IIIA receptor inhibitor will improve the blood circulation; following ischemia by preventing vessel reocclusion by distally progressing clot fragments. We studied the effects of the novel GP IIB/IIIA antagonist in combination with recombinant tissue plasminogen activator (rtPA), to assess the role of activated platelets in perfusion deficits following ischemic stroke. **Methods and results:** Sprague-Dawley adult male rats were anesthetized to undergo distal right mid-

dle cerebral artery (MCA) occlusion and Evans Blue dye was injected via jugular vein to visualize perfused microvessels. After embolization, rats were treated intravenously with saline, GP IIb/IIIa antagonist (bolus 6mg/kg), rtPA (bolus 10mg/kg) and combination of GP IIb/IIIa with rtPA. Our data indicated that GP IIb/IIIa antagonist treated animals had reduced perfusion deficits but not statistically significant when compared to saline treated rats, however combination treatment with rtPA ( $p=0.001$ ) and rtPA alone ( $p=0.003$ ) significantly reduced the perfusion deficits and neurological deficits as well. Most of the cerebral microvessels of cortex and striatum were reopened in the combination therapy, compared with saline treated group. **Conclusion:** rtPA alone and in combination with GP IIb/IIIa receptor inhibitor significantly reduces the perfusion deficits and improves the neurological outcomes. Patency of cerebral microvessels most likely contributes to the benefits observed with this combination therapy.

**20 POLYMER BASED NANO-CARRIERS FOR THE SOLUBILIZATION AND DELIVERY OF MULTI-DRUG RESISTANCE MODULATORS**

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**Purpose:** To enhance the effectiveness of MDR modulators in cancer therapy through development of a long circulating delivery system based on polymeric micelles of poly (ethylene oxide)-*block*-poly (ε-caprolactone) (PEO-*b*-PCL). **Methods:** PEO-*b*-PCL block copolymers were synthesized by ring opening polymerization of ε-caprolactone using methoxy polyethylene glycol (5000 g mol<sup>-1</sup>) and stannous octoate as initiator and catalyst, respectively. The feed ratio of ε-caprolactone to initiator was changed to achieve different PCL block lengths. Prepared block copolymers were characterized for their average molecular weight by <sup>1</sup>HNMR and gel permeation chromatography. An optimized method has been developed to achieve PEO-*b*-PCL micelles of < 100 nm capable of efficient drug encapsulation. Cyclosporine A (CyA) was used as a model MDR modulator for encapsulation in PEO-*b*-PCL. Micellar size and levels of drug encapsulation was determined by light scattering and HPLC, respectively. The pharmacokinetic of free and encapsulated CyA was assessed in healthy animals. Male Sprague-Dawley rats were catheterized under halothane anaesthesia a day before the experiment. Isotonic solutions of CsA in polymeric micelles and its standard IV formulation, Sandimmune®, were injected into the right jugular vein of the animals. Serial blood samples were obtained from the cannula for up to 48h and assayed for drug by HPLC. Pharmacokinetic parameters (mean ± SD) such as area under the plasma concentration vs time curve (AUC), volume of distribution (V<sub>d</sub>), clearance (CL), and half-life (t<sub>1/2</sub>) were determined for each group and com-

pared by unpaired t test. **Results:** PEO-*b*-PCL block copolymers with PCL number average molecular weights of 5000, 13000 and 24000 g mol<sup>-1</sup> were prepared and assembled to micelles of 60- 80 nm in size. The average diameter of prepared micelles increases to 100-120 nm after drug loading. Aqueous solubility of CyA reached a level of 1.3 mg/mL by PEO-*b*-PCL micelles, compared to a concentration of 14 mg/mL in the absence of the block copolymer. Non compartmental pharmacokinetic analysis of our data showed a significant increase in AUC (25.68301 ± 5.63 vs. 33.147 ± 3.35, P< 0.05); a decrease in the volume of distribution (V<sub>d</sub>) (2.47 L/Kg vs 0.85 L/Kg, P< 0.001) and a decrease in clearance (CL) (0.17 L/Kg/h vs 0.07 L/Kg/h, P< 0.01) for polymeric micellar formulation compared to free drug. The change in the biological half-life was not significant (P>0.05). **Conclusion:** PEO-*b*-PCL copolymers can efficiently encapsulate and change the pharmacokinetic profile of the CyA. This may lead to reduced pharmacokinetics interactions with anticancer agents as well as decreased toxicity and improved efficacy for CyA.

**21 IS HALOFANTRINE A CYP3A SUBSTRATE IN RAT? STEREOSPECIFIC LIVER AND INTESTINAL MICROSOMAL STUDIES**

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**Purpose:** To determine if the metabolism of the enantiomers of the chiral drug halofantrine (HF) to its major circulating metabolite, desbutylhalofantrine (DHF), was facilitated by CYP3A in rat liver and intestine. **Methods:** Intestinal and hepatic microsomal protein was isolated from four Sprague-Dawley rats using ultracentrifugation. For incubations microsomal protein (1 mg/mL) was incubated in phosphate buffer (pH 7.3)/MgCl<sub>2</sub>, containing ascending concentrations of (±)-HF (500 to 100000 ng/ml), at 37°C. NADPH (1 mM) was used as a cofactor and the reaction was stopped by adding acetonitrile after 15 min. The DHF enantiomer was measured using stereospecific HPLC. The V<sub>max</sub> and k<sub>m</sub> were calculated for each rat liver and intestinal sample using nonlinear regression analysis and the Michaelis Menten equation. Four concentrations of ketoconazole (KTZ), a selective inhibitor of CYP3A4 in humans was co-incubated with HF in the inhibition studies. **Results:** Kinetic parameters of DHF formation were as follows:

Tissue	V <sub>max</sub> , pmol/mg/min			k <sub>m</sub> , μM		
	(+)	(-)	(-):(+ ratio	(+)	(-)	(-):(+ ratio
Liver	51.1±18.0 <sup>a</sup>	72.5±32.8 <sup>a</sup>	1.38±0.18 <sup>bc</sup>	25.5±7.97 <sup>ab</sup>	20.9±6.47 <sup>a</sup>	0.81±0.10 <sup>c</sup>
Intestine	24.3±3.58	21.7±6.16	0.88±0.15	51.5±10.1	43.8±15.9	0.85±0.26

a.) p<0.05 vs intestine b.) p<0.05 vs. (-) enantiomer c.) p<0.05 compared to unity

Catalytic rate was higher in liver than intestine. Further, intestinal k<sub>m</sub> was lower than liver, which may reflect a difference in the tissue composition of CYP isoenzyme. Stereospecificity was observed in V<sub>max</sub> and k<sub>m</sub> of liver, whereas intestinal V<sub>max</sub>



and km were non-stereoselective. This lends further support to tissue-specific differences in the CYP composition involved in HF metabolism. For the inhibition studies involving liver, increasing KTZ concentrations caused a progressive increase in the inhibition of metabolism to both DHF enantiomers. In intestine, significant inhibition was observed when comparing controls to the lowest concentration of KTZ. Above this concentration, however, no further inhibition was observed. **Conclusions:** In rat, both HF enantiomers appear to be metabolized by hepatic and intestinal CYP3A. The difference in km and degree of stereoselectivity in DHF formation suggests tissue-specificity in CYP composition. More than one CYP isoenzyme appears to be involved in metabolism of HF to DHF. **Acknowledgements:** Merck Company Foundation National Summer Student Research Program (SS). The authors thank Ms. Daniella Skeith for her technical assistance.

## 22 THE ROLE OF CYP3A IN THE IN VITRO BIOTRANSFORMATION OF AMIODARONE TO DESETHYLAMIODARONE IN THE RAT

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**Purpose:** Amiodarone(AM) is a very lipophilic antiarrhythmic agent that is a substrate of CYP3A4 in humans. Desethylamiodarone (DEA), its primary active metabolite is formed by human liver and intestinal CYP3A4. In order to establish the rat as a suitable model for preclinical metabolism studies involving AM, we conducted a study to ascertain the role of rat CYP3A in its hepatic and gut metabolism. **Methods:** Liver and jejunum (10 cm length) tissues were harvested from five male Sprague-Dawley rats. After isolation of microsomal protein, incubations were performed with AM, in the presence and absence of ketoconazole (KTZ), which is a specific inhibitor of human CYP3A4. The incubation mixture consisted of different amounts of AM, rat microsomal protein (1 mg/mL), NADPH (1 mM) and MgCl<sub>2</sub> in phosphate buffer solution (pH=7.4). Incubations were performed over the linear range of DEA formation (30 min) at 37°C. HPLC was used to determine concentrations of AM and DEA. The Michaelis-Menten equation and nonlinear fitting was used to determine V<sub>max</sub> and K<sub>m</sub>. **Results:** Tissue specificity was observed in the formation of DEA by microsomal protein.

Tissue	V <sub>max</sub> , pmol/mg protein/min	km, μM
Liver	106.5±28.3 <sup>a</sup>	32.3±19 <sup>a</sup>
Jejunum	23.7±9.4	46.9±13.2

a. Significantly different (p<0.05) compared to jejunum

Liver was more efficient in metabolism of AM than jejunum: Upon incubation with KTZ, progressive reductions in DEA formation were seen, with maximum decreases of 87% and 54% being observed in liver and gut tissues, respectively. Compared

to jejunum, the inhibitory effect in liver was more progressive and pronounced than in gut. Incubation with rat anti-CYP3A2 caused a reduction in metabolism by liver but not intestinal microsomes. **Conclusion:** The CYP isoform(s) involved in metabolism of AM to DEA in liver appear to be qualitatively and qualitatively different from that in intestine. KTZ was an effective inhibitor of the dealkylation of AM by both rat liver and intestinal microsomes, therefore suggesting that CYP3A is involved in the metabolism of AM of rat as well as human.

## 23 DO STATINS REVERSE THE DOWN-REGULATING EFFECT OF INFLAMMATION ON β-ADRENERGIC RECEPTORS? A PRELIMINARY REPORT ON PRAVASTATIN-PROPRANOLOL INTERACTION

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**Purpose.** The use of the Early Adjuvant Arthritis (EAA) model in the rat as a model of inflammation that offers less suffering, yet exhibits a Th1 skewed immune response. It has been shown that an inflammatory state can reduce the electrocardiographic (ECG) response of cardiac β-adrenergic receptors to propranolol. We hypothesize that pravastatin, a hydroxymethylglutaryl coenzyme A reductase inhibitor (statin) reverses the ability of the inflammatory state to diminish cardiac response to the β-blocking drug propranolol, and that it may correct the Th1/Th2 immune balance. **Methods.** Four groups of male Sprague-Dawley rats were either administered EAA and statin (n=13), EAA and placebo (n=13), placebo-EAA and statin (n=11), or placebo-EAA and placebo-statin (n=14). Metal electrodes were implanted into rats the day prior to ECG measurement periods. The PR interval response to propranolol was measured at 0, 20, 40, 60, 80, 100, 140, 180, and 240 min on days zero, four and eight. On day zero, rats received 38 mg/kg of *Mycobacterium butyricum* or placebo by injection into the base of the tail. On day 4, a regimen of twice daily 6 mg/kg of pravastatin, or placebo, was commenced. On day 8 the final ECG measurement was performed. Blood samples were obtained on days 0, 4, and 8. **Results:** On day 0, propranolol significantly prolonged PR-interval over all time points [mean ± SEM (1104±135) area under the percentage change from baseline-time curve (AUEC)]. On day 8, the untreated EAA group demonstrated significant reduction in response to propranolol (AUEC, 302±266 percentage.min). Treatment with pravastatin reversed AUEC in EAA to close to the normal values (1573±413 percentage.min). **Conclusion:** Pravastatin appears to reverse the effects of inflammation on propranolol induced PR-interval response in the rat. Patients with inflammatory conditions, such as rheumatoid arthritis or post-myocardial infarction, may benefit from the use of statins during cardiovascular treatment. Supported by the CIHR and RX&D Health Research Foundation.

#### 24 CYCLIC AMP LEVELS IN THE RAT HEART IN RESPONSE TO ACUTE AND CHRONIC INFLAMMATION

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**Purpose:** Inflammation has been shown to reduce drug response. Cyclic AMP (cAMP) is the major intracellular second messenger produced after drug activation of g-protein coupled receptors. The purpose of this study was to investigate if cAMP production is changed in the rat heart in the presence of both acute inflammation (interferon  $\alpha$ 2a) and chronic inflammation (adjuvant arthritis). **Methods:** Male Sprague-Dawley rats (n=3 per group) were injected with 0.2ml of either 100,000 IU of interferon  $\alpha$ 2a subcutaneously (sc), 10mg of heat-inactivated *Mycobacterium butyricum* in tail base, or placebo (sterile normal saline sc and tail base). Hind paw and neutrophils were assessed for presence of inflammation and rats were sacrificed and the heart extracted and frozen immediately in liquid nitrogen. The heart was ground into fine powder using mortar and pestle, and cAMP extracted in 0.1N HCL. The homogenate was centrifuged at 600g for 10 minutes and the supernatant removed and assessed for cAMP content using an immunoassay kit. **Results:** Neither acute nor chronic inflammation had a significant effect on rat heart cAMP production. In acute inflammation, mean cAMP concentration was  $2.29 \pm 0.24$  pmol/mg of tissue in interferon treated, which was not significantly different from  $2.31 \pm 0.17$  pmol/mg observed in placebo (control) rats (p d<sup>n</sup> 0.951). In chronic inflammation, the mean cAMP concentration was  $1.82 \pm 0.24$  pmol/mg of tissue, which was not significantly different from  $1.56 \pm 0.13$  pmol/mg observed for the placebo group (p d<sup>n</sup> 0.39). **Conclusion:** A change in cAMP production is not one of the mechanisms involved in inflammation-induced down-regulation of g-protein coupled receptors. **Acknowledgements:** This investigation was supported by CIHR.

#### 25 RAT STRAIN DIFFERENCES IN RESPONSE TO CARDIOVASCULAR DRUGS

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**Purpose.** Inflammatory conditions decrease cardiovascular (CV) response to b-adrenergic and calcium channel blockers, which may be one of the reasons behind the therapeutic failure observed in cardio-inflammatory states. Animal models, such as the inflamed Sprague-Dawley (SD) rat, have been used to show that the potency of sotalol to prolong QT and PR interval is decreased in the presence of acute inflammation. However, the rats used have been normotensive. The purpose of this study was to examine whether the Spontaneously Hypertensive Rat

(SHR), and its normotensive counterpart, the Wistar Kyoto Rats (WKY), are more realistic models to study the effect of inflammation on CV drugs as compared to the SD rats. **Methods.** Three strains of rats, SHR (n=11), WKY (n=12), and SD (n=8) were obtained. Stainless steel teflon-coated wires were inserted surgically in the left and right axial regions of the rat for the determination of the rat electrocardiogram (ECG). Each strain was divided into 2 groups; one group received saline (control) and the other received interferon  $\alpha$ 2A subcutaneously at 0 and 9 h (inflamed). 3 h after the 2<sup>nd</sup> injection, the rats were dosed with 80 mg/kg sotalol and QT and PR interval were measured up to 6 h. The area under the % change from baseline vs. time (AUEC) was calculated for each ECG parameter and statistical comparison was made between inflamed and their respective control groups. **Results:** As expected, inflammation significantly reduced response to sotalol in SD rats with respect to PR (p = 0.046) and QT (p = 0.01) intervals. Inflammation also resulted in a reduced AUEC of QT intervals in WKY (p = 0.004) but had no significant effect on AUEC of PR interval in this strain. Sotalol failed to prolong either PR or QT interval in SHR in both control and inflamed group. **Conclusions:** ECG data indicates strain differences between SHR, WKY and SD in their responsiveness to b-adrenergic blocker sotalol, independent of the hypertensive state. Differences in expression of pro-inflammatory mediators and b-receptor density may be responsible for the observed differences. Normotensive SD rats best mimic the observation previously made with regard to ECG in human rheumatoid arthritis. Supported by CIHR

#### 26 THE EXTENT OF RENAL EFFECTS OF NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS) IS PHARMACOKINETIC-DEPENDENT

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**Purpose.** Cyclooxygenase (COX) is the key enzyme forming arachidonic acid to prostaglandins. COX-1 and COX-2 are two different isoforms of cyclooxygenase that are inhibited by NSAIDs. Rofecoxib and meloxicam are COX selective NSAIDs. The use of NSAIDs has been associated with renal side effects such as impaired glomerular filtration rate and/or a decreased in urinary sodium and potassium excretion. We have previously reported that among a selected group of NSAIDs, only meloxicam is void of renal effect. Here, we tested our hypothesis that the relative distribution into kidneys of two COX-2 selective NSAIDs, rofecoxib and meloxicam, determine their degree of kidney effect. **Methods.** Rofecoxib (10 mg/kg, n=7) or meloxicam (3 mg/kg, n=5) was administered orally as single doses to rats that were catheterized in the right jugular vein for serial (0-24 h post-dose) blood collection. Urine was collected (0800-1600 h) the day before and after dosing. Rats

were sacrificed 24 h post-dose, kidneys removed, homogenized. Renal function was assessed by measurement of urinary sodium excretion rate using neutron activation analysis. High-performance liquid chromatography was used for determination of NSAIDs in plasma and kidney homogenates. **Results.** Pharmacokinetic patterns of the NSAIDs were in agreement with those reported earlier. Treatment with rofecoxib significantly decreased sodium excretion rate from  $0.35 \pm 0.02$  to  $0.13 \pm 0.01$  mol/min/100g ( $p < 0.01$ ). Meloxicam did not significantly influence sodium excretion rate ( $0.49 \pm 0.06$  vs.  $0.38 \pm 0.05$  mmol/min/100g,  $p > 0.3$ ). There was no significant association between area under plasma rofecoxib concentration-time curve and renal effect. Mean concentrations of rofecoxib and meloxicam at 24 h post-dose were  $103 \pm 32$  and  $4851 \pm 1281$  ng/mL, respectively. Rofecoxib concentrations 24 h post-dose were significantly associated with the observed sodium excretion rate ( $r = 0.95$ ,  $p < 0.0012$ ). The ratio of kidney to plasma concentration was 1.69 and 0.35 for rofecoxib and meloxicam, respectively indicating less distribution into kidneys for the latter. **Conclusion.** Administration of rofecoxib causes reduced sodium urinary excretion. The extent of the side effect is correlated with the 24-h post dosing drug concentration. This is suggestive of a deep-tissue distribution-dependence mechanism for the side effect. A high trough rofecoxib concentration may predict emergence of kidney side effect for this NSAID.

## 27 EFFECT OF EARLY ARTHRITIS ON HEPATIC CYP ENZYMES AND PHARMACOKINETICS OF VERAPAMIL: A NEW APPROACH TO THE USE OF AN ANIMAL MODEL OF INFLAMMATION FOR PHARMACOKINETIC STUDIES

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**Purpose.** Adjuvant-induced arthritis (AA) is a well-established model of chronic inflammation in rats, with symptoms of polyarthritis and inflammation developing typically 12 to 14 days post-adjuvant. While this model of inflammation has been used extensively to study pharmacodynamics and pharmacokinetics of drugs, it subjects animals to significant pain. To avoid unnecessary suffering of animals, we evaluated the suitability of the early phase of this model (0 to 7 days prior to disease onset) for pharmacokinetic studies involving inflammatory conditions. Inflammation reduces oral clearance of drugs that are efficiently metabolized in the liver. **Methods.** Male, Sprague-Dawley rats were injected with 10 mg *Mycobacterium butyricum* (AA) or sterile saline (Control) into the tail base on day 0. Blood was sampled on days 0, 1, 3, 5 and 6 for determination of serum nitrite and C-reactive protein (CRP) as markers of inflammation. Animals were weighed and paw thickness were measured prior to blood sampling on each sampling day to

monitor for symptoms of arthritis. One set of AA ( $n=4$ ) and Control ( $n=6$ ) animals were cannulated in the right jugular vein on day 5, and administered an oral dose of 20 mg/kg racemic verapamil on day 6. Serial blood samples were collected and S and R verapamil concentrations were determined by a stereospecific HPLC method. Hepatic cytochrome P450 content was measured in a second set of AA ( $n=4$ ) and Control ( $n=4$ ) animals sacrificed on day 6. **Results.** AA rats gained significantly less weight than Controls but no signs of joint deformity or changes in paw thickness were observed. Serum CRP levels were significantly elevated and were highest 1 day after injection of adjuvant compared with healthy rats ( $640 \pm 137$  mg/mL vs.  $366 \pm 90$  mg/mL,  $p=0.001$ ). Serum nitrite concentrations were also significantly elevated on day 1 ( $62 \pm 20$  mmol vs.  $24 \pm 9$  mmol,  $p=0.001$ ) and were highest on day 6 ( $109 \pm 38$  mmol vs.  $35 \pm 10$  mmol,  $p < 0.001$ ). Plasma concentrations of S and R verapamil were significantly elevated in AAs as compared with Controls.  $C_{max}$  and  $AUC_{0-4}$  for S-verapamil in AA rats were 6.7 and 9.3-fold higher than in Control rats. For R-verapamil,  $C_{max}$  and  $AUC_{0-4}$  in AA rats were 3.6 and 9.5-fold higher than in Control rats. Hepatic cytochrome P450 content was significantly reduced in AA rats compared with Control rats ( $0.334 \pm 0.091$  nmol/mg protein vs.  $0.651 \pm 0.037$  nmol/mg protein,  $p=0.001$ ). **Conclusion.** Our data demonstrate that the inflammatory process begins within days of adjuvant administration as marked by significantly increased CRP and nitrite serum concentrations, reduced hepatic cytochrome P450 content and corresponding reduced verapamil clearance. We conclude that early adjuvant arthritis is a suitable model of inflammation for pharmacokinetic studies that avoids unnecessary exposure of animals to pain and suffering of fully developed adjuvant arthritis. This work supported by the Canadian Institutes of Health Research.

## 28 AN ENCAPSULATION TECHNIQUE FOR HIGHLY WATER SOLUBLE DRUGS: DRUG LOADING AND RELEASE STUDIES

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**Purpose:** The main aim of the present study was to assess formulation parameters to enhance incorporation of highly water-soluble drugs into poly (D,L-lactic-co-glycolic acid) (PLGA) microspheres. Mainly, water insoluble drugs have been incorporated into the particulate carriers using different encapsulation techniques with typical drug content values. However, these techniques suffer the drawback of a poor incorporation efficiency of water-soluble drugs due to rapid migration and therefore loss of drug into the aqueous phase. Urea was used as a

drug model. **Method:** Drug-loaded PLGA microspheres were prepared by the o/w solvent evaporation technique. Drug was added into methylen chloride. The resulting solution was poured into a PVA solution and emulsified. This mixture was then stirred to complete solvent evaporation. Microspheres were collected by centrifugation, washed with distilled water, freeze-dried and stored at  $-20^{\circ}\text{C}$ . For morphological examinations, microspheres were analysed by Scanning Electron Microscopy after being fixed on a sample support and gold metalized. The particles size and size distribution were determined by laser light diffractometry. Encapsulated drug was measured by UV-Spectrophotometry after breaking the microspheres in methylen chloride. Drug release and its stability were evaluated. **Results:** The size range of microspheres spanned 1-4  $\mu\text{m}$  and the mean size was measured  $2.6 \pm 0.6 \mu\text{m}$ . By Scanning Electron Microscope, the microspheres appeared to be spherical and non-aggregated and the particle surface seemed to be smooth. The prepared microspheres were stable during the storage and there was no coagulation. **Conclusions:** As, there are some problems to prepare the microspheres containing highly water-soluble drugs, this microencapsulation process can be useful to encapsulate these drugs.

#### 29 RAPAMYCIN-LOADED NANOPARTICLES PREPARED BY SOLVENT EVAPORATION TECHNIQUE: DRUG LOADING AND CHARACTERIZATION

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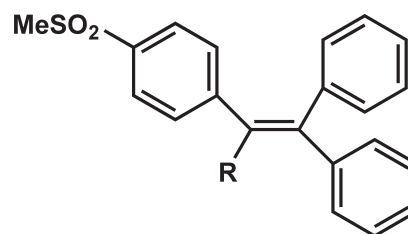
**Purpose:** The potent immunosuppressive drug, rapamycin, inhibits T cell activation and proliferation. It binds to FK-binding protein 12 in the cells. The purpose of this study was to load rapamycin in poly (D,L-lactic-co-glycolic acid) (PLGA) nanoparticles and to characterize the nanoparticles. **Methods:** Rapamycin nanoparticles were prepared by the o/w solvent evaporation technique. Rapamycin was dissolved in chloroform and then emulsified in an aqueous solution of polyvinyl alcohol (PVA) by sonication. Then the emulsion was added into PVA solution and stirred to evaporate chloroform. The final emulsion was centrifuged and the precipitate was washed with distilled water, freeze-dried and the nanoparticles stored at  $-20^{\circ}\text{C}$  for future studies. Nanoparticle size and size distribution was determined by dynamic light scattering. The encapsulation of rapamycin in nanoparticles was measured by HPLC-UV analysis after extraction of rapamycin from nanoparticles. Release study of rapamycin from nanoparticles was evaluated at different time points. **Results:** The mean particle size was determined 263.2 nm with a polydispersity 0.01 for empty nanoparticles and 275.9 nm with a polydispersity 0.07 for rapamycin-loaded nanoparticles. The lower limit of detection for HPLC method was measured 2ng/ml. Encapsulation effi-

ciency of rapamycin in nanoparticles was about 70%. **Conclusion:** Rapamycin is effectively encapsulated in PLGA nanoparticles. The HPLC method developed was suitable for the analysis of rapamycin in PLGA nanoparticles.

#### 30 DESIGN OF ACYCLIC TRIARYL OLEFINS: A NEW CLASS OF POTENT AND SELECTIVE CYCLOOXYGENASE-2 (COX-2) INHIBITORS

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**Purpose.** The primary objective of this investigation was to design a novel class of selective COX-2 inhibitors in which the traditional heterocyclic or carbocyclic central ring template is replaced by an olefinic scaffold. This drug design concept is based on the hypothesis that the stereochemical disposition of aryl/alkyl substituents relative to the C=C bond to which they are attached controls COX-2 inhibitory potency and selectivity where the function of the C=C is to provide the necessary substituent geometry about the C=C bond that allows an optimal protein-ligand interaction in the COX-2 active site. **Methods.** A group of 1,1-diphenyl-2-(4-methanesulfonylphenyl)-2-alkyl-1-ethenes **1** were synthesized using a McMurry olefination reaction that involved the titanium-catalyzed reductive cross-coupling of an alkylphenone with benzophenone that afforded the target acyclic products in high chemical yield. **Results.** In vitro enzyme immuno assay data showed that the most potent and selective compound **1** (R = *n*-Bu), among the group of compounds evaluated, was a highly potent (COX2  $\text{IC}_{50} = 0.014 \mu\text{M}$ ; COX-1  $\text{IC}_{50} > 100 \mu\text{M}$ ) and selective [COX-2 selectivity index (S.I.) > 7142] COX-2 inhibitor. A molecular modeling docking study showed that **1** (R = *n*-Bu) binds in the center of the COX-2 binding site and that the  $\text{MeSO}_2$  moiety is inserted deep into the COX-2 secondary binding pocket. **Conclusions.** (i) A rational drug design approach was used to identify a new class of achiral triaryl olefins **1**, that (ii) were synthesized via a short two-step reaction sequence in 62-76% yield, that (iii) possess identical C-1 phenyl substituents that precludes the possibility of (*Z*)- and (*E*)-stereoisomers, which (iv) exhibit highly potent and COX-2 inhibitory activity.



**1**, R = Me, Et, *n*-Bu, *n*-Pentyl, *n*-Hexyl, *n*-Nonyl, *n*-Pentadecyl

31 HYBRID CALCIUM CHANNEL MODULATORS WITH NITRIC OXIDE RELEASE PROPERTIES AS PRODRUGS FOR THE POTENTIAL TREATMENT OF CONGESTIVE HEART FAILURE

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**Purpose:** the synthesis and evaluation (*in vitro*) of ten different tissue selective calcium channel (CC) modulators, that exhibit a dual cardioselective CC agonist effect, in conjunction with a smooth muscle CC antagonist vasorelaxant effect, which would satisfy the clinical requirements for the treatment of congestive heart failure (CHF). Furthermore, we attached to these drugs an enzymatically labile nitric oxide releasing group, which upon metabolism, would decompose to give up to two moles of nitric oxide per mole of prodrug. **Methods:** the chemical synthesis of these prodrugs was achieved by the one pot reaction between the corresponding 4-aryl-1,4-dihydro-2,6-dimethyl-5-nitro-3-pyridine carboxylic acids, and a mesylate derivative. The smooth muscle CC antagonist activity was determined as the micromolar concentration of the test compound, required to produce 50% inhibition of the muscarinic receptor-mediated (carbachol) Ca<sup>2+</sup>-dependent contraction of guinea pig ileum longitudinal smooth muscle (GPIISM). The cardiac calcium channel agonist effect was calculated as the percentage increase in contractile force of isolated guinea pig left atrium (GPLA) relative to its basal contractile force in the absence of test compound. The nitric oxide release was determined *in vitro* by quantification of nitrite produced by the reaction of nitric oxide with oxygen and water using the Griess reaction, in the presence of either pig liver esterase or guinea pig serum. **Results:** with the exception of compounds having a 2-pyridyl at the 4- position of the 1,4-DHP ring, all compounds showed selective calcium channel modulation activity, that is, they exhibited the desired dual cardioselective CC agonist effect in conjunction with a smooth muscle CC antagonist vasorelaxant effect. Interestingly, they were stable in physiological conditions (PBS pH 7.4 at 37°C for 1.5 h), releasing nitric oxide only upon addition of either pig liver esterase or guinea pig serum. **Conclusions:** a) These results give additional evidence to support the fact that it is possible to achieve selective calcium channel modulation activities, by increasing the force of the heart contractions and inducing peripheral vasodilation (*in vitro*); b) based on many reports on the literature, in which is described the importance of nitric oxide for the maintenance of blood-vessel homeostasis, blood pressure, and organ perfusion, the enzymatic release of nitric oxide from these prodrugs could further improve their usefulness towards the clinical treatment congestive heart failure. **Acknowledgments:** We are grateful to the Canadian Institutes of Health Research for financial support of this research (Grant No. MT-8892), and to the National Council of Science and Technology (CONACYT, Mexico).

32 GROWTH SUPPRESSION OF HAMSTER FLANK GLANDS BY TOPICAL APPLICATION OF ARTOCARPIN

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**Purpose:** We investigated the *in vivo* effect of Artocarpin; a 5 $\alpha$ -reductase (5 $\alpha$ -R) inhibitor, on the growth suppression of androgen-dependent hamster flank glands. The inhibition of 5 $\alpha$ -R might be a relevant approach for therapeutic treatment of androgen-dependent diseases, such as androgenic alopecia, benign prostate hyperplasia and acne. **Methods:** Artocarpin was isolated from a traditional Thai plant *Artocarpus incisus* by ether extraction. Its purity was determined by NMR and IR. 8 weeks' old prepubertal male Syrian golden hamsters were used for the animal study. The hair on the lower back was clipped weekly to expose the flank glands; only one side of flank organ was treated in each animal. 20  $\mu$ l of treatment solution contained either (a) vehicle alone (95% ethanol/PEG (80/20)), (b) Artocarpin, (1.0, 0.5, 0.1 mg) or (c) Flutamide, (1.0 mg). The duration of the experiment was 30 days with one administration per day. At the end of experiment, the growth of both flank glands was determined. **Results:** All treatment groups containing Artocarpin showed a statistically significant ( $P < 0.05$ ) suppression on the growth of the hamster flank glands compared to the control group. The contralateral flank glands were also affected. These effects were also seen in the treatment group with Flutamide. 1 mg Artocarpin had an equal effect compared to 1 mg Flutamide that is an androgenic receptor blocker. **Conclusion:** The *in vivo* results show that Artocarpin inhibits the growth of hamster flank glands. This is due to the inhibition of 5 $\alpha$ -reductase which converts testosterone to 5 $\alpha$ -dihydrotestosterone which is linked to the flank organ growth. This has important implications for the treatment of androgenic alopecia, benign prostate hyperplasia and acne.

33 CELL TOXICITY STUDIES OF BIORELEVANT DISSOLUTION MEDIA USING CACO-2 CELLS

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**Purpose:** The Caco-2 model is a widely used tool in predicting absorption of oral drug candidates. The drug permeability is usually tested in Hanks' Balanced Salt Solution as transport medium. However this medium is not suitable for poorly soluble drugs. We investigated the toxicity of two biorelevant dissolution media (BDMs) which simulate the physiological conditions in gastrointestinal tract as transport medium. These media have shown that they are able to increase the solubility of

poorly soluble drugs. **Methods:** Fasted state (FaSSIF) and Fed state (FeSSIF) simulated small intestinal fluid were made using two chemical grades of the major ingredients sodium taurocholate (TC) and egg-lecithin (EL) (TC: LQ=crude; HQ=97% purity and EL: LQ=60%; HQ=90% purity). Each batch of BDMs was split into two parts. One part was freeze-dried the other part was immediately used. The Caco-2 cells were seeded into 96-well plates at 1000 cells/well and incubated in 37°C, 5% CO<sub>2</sub> for 1 week. 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2H tetrazolium bromide (MTT) assay was used to test the toxicity. The cell monolayers were exposed to the BDMs at various pH, concentrations of bile salts and lecithin for different time interval. **Results:** There was no significant difference in the cell toxicity between non-freeze dry and freeze dry BDMs. The HQ FaSSIF with no dilution showed a toxic effect at pH 6.5 and 7.4 within 1 hour. However, a serial diluted (5, 10 and 15 times) HQ FeSSIF and a dilution of 2, 4 and 8 times HQ FaSSIF media showed no toxic effect within 1 hour using different physiological pH values. LQ media showed at all concentrations toxic effects. **Conclusions:** Dilutions of HQ FeSSIF have no toxic effect on the Caco-2 system. This media seems to be suitable to be used as transport media for poorly soluble drugs in the Caco-2 system.

#### 34 EVIDENCE FOR IN VITRO CELLULAR UPTAKE OF A DERIVATIZED $\beta$ -CYCLODEXTRIN DRUG CARRIER AND ITS POTENTIAL METABOLITE

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**Purpose:** Cyclodextrins (CyDs) are relatively large, polar molecules (1000 to over 1500 Da) that are generally considered poor permeants of biological membranes. Entry of CyDs into cells is critical to their use as drug carriers and solubilizing components in drug formulations. Confocal laser scanning microscopy (CLSM) is a powerful technique for observing the permeation of fluorescent derivatives across cell membranes. This project was designed to determine whether or not b-CyD can cross the cell membrane. **Method:** b-CyD-6-NH<sub>2</sub> and 6-aminoglucose were coupled to 4-chloro-7-nitro-benzofurazan (NBD-Cl), and purified by C18 RP HPLC using methanol-water gradient elution. HepG2 (human hepatocellular carcinoma) cells were grown in MEM medium. The cellular uptake studies of the resulting fluorescent compounds, NBD-b-CyD and NBD-glucose, were performed at different time points under cell growth conditions. The cell membrane was stained by a red fluorescent dye, to demonstrate integrity of the cell membrane, and cell nuclei were stained with a purple fluorescent dye (Dapi). **Results:** Cytoplasm was diffusely and granularly stained by the green-fluorescing NBD-b-CyD and NBD-glucose, but no green fluorescence was visible in the nuclei. The

diffusion patterns of both compounds had no significant differences, even at different uptake time points. **Conclusion:** These data indicate that both NBD-b-CyD and NBD-glucose enter cells via diffusion, but these experiments do not eliminate the possibility that trace fluorescent degradation products are responsible for fluorescence seen after incubation with NBD-b-CyD, even though NBD-b-CyD and NBD-glucose are stable in control conditions.

#### 35 EFFICIENT PROTEIN SEPARATIONS USING SURFACTANT-BASED COATINGS IN CAPILLARY ELECTROPHORESIS

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**Purpose:** In capillary electrophoresis, surface coatings are essential for protein separations to prevent adsorption. Surfactant-based coatings are attractive due to their versatility, simplicity, and low cost. Double chain cationic surfactants such as didodecyldimethylammonium bromide (DDAB) adsorb onto the capillary to form semi-permanent bilayer coatings. These coatings are effective in the separation of cationic proteins. This presentation will discuss the factors affecting the coating stability, and demonstrate how high stability coatings can be achieved. **Methods:** Studies are performed on a Beckman P/ACE CE. Coatings are generated simply by flushing the capillary with surfactant solution for 10 min, followed by a 3-minute rinse with buffer to remove excess surfactant. **Results:** Factors such as ionic strength increase the coating stability by decreasing the critical micelle concentration (cmc) of the surfactant solution. Using optimized conditions such as 50 mM Acetate buffer at pH 5.0 in a 25 mm capillary i.d., cationic proteins were separated using DDAB coatings with efficiencies of 1.05 million plates/m and reproducibility better than 0.8% RSD. Another means of lowering the surfactant cmc is to increase the length of its hydrophobic chain. Using ditetradecyldimethylammonium bromide coating in 50 mM ammonium formate buffer at pH 4.5, protein separations can be achieved in about 2 min with efficiencies of 1.4 million plates/m. The stability of these long chain surfactants was very high with reproducibility less than 0.7% RSD within the day, and less than 1.23% RSD from day-to-day (5 days), without the need to recoat the capillary between runs. **Conclusions:** Careful control of instrumental and chemical factors enables generation of highly efficient coatings for protein separations simply by flushing a surfactant solution through the capillary in CE.

#### 36 QUALITATIVE AND QUANTITATIVE ANALYSIS OF THE CANNABINOID CONTENT OF COMBUSTED CANNABIS PLANT TISSUE

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**Purpose:** Investigations were carried out to develop a method and study the volatile constituents of combusted marijuana plant material in a semi-enclosed environment. The most common way of ingesting marijuana in human has been by smoking, thus it is essential to be able to evaluate the cannabinoid content of the combustion products of cannabis tissue. **Methods:** Under license and permit from Health Canada, cannabis plant material was combusted and the resultant smoke captured and analyzed using solid phase extraction and HPLC with either UV or MS detection. This procedure was repeated at least 3 times for each sample weight. The resulting methanol extracts were then analyzed using a reverse phase chromatography method with a C8 column and a mobile phase consisting of 65% acetonitrile, 35% water containing 0.04% formic acid. The detection wavelength was set at 230nm. **Results:** It was clearly shown that 50% of the tetrahydrocannabinolic acid (THCA) in the raw plant material was converted to delta 9 tetrahydrocannabinol (THC) with smaller amounts of cannabidiol (CBD), cannabinol (CBN) and cannabichromene (CBC) also being formed. What was unexpected is the fact that in every sample analyzed, a 50% recovery of THC compared to the original THCA content was noted. Numerous experiments were done to show that the chemical constituents of cannabis were being captured and not lost to the external environment. Pure samples of CBD, CBN and THC were analyzed using the combusted technique above and all showed 90% or greater recovery at a range of concentrations. **Conclusions:** A reliable method for both qualitative and quantitative determination of cannabinoid compounds in combusted cannabis plant material was developed. It clearly demonstrated that the majority of THCA is converted to THC with smaller amounts of CBD, CBN and CBC being formed as well.

### 37 ISOLATION AND CHARACTERIZATION OF PROBIOTICS FROM CALF FECES FOR THE TREATMENT OF DIARRHEA

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**Purpose:** To identify potential probiotics for the treatment of diarrhea in neonatal calves. The ideal candidates would be lactic acid bacteria (LAB) that are stable in high concentrations of bile and low pH. They would also produce predominantly L-lactate, thus preventing exacerbation of the D-lactic acidosis that occurs in many calves with diarrhea. **Methods:** Fecal samples were collected from 13 healthy calves. Serial dilutions were plated on MRS agar. Randomly selected colonies were gram stained and subcultured onto MRS agar. To determine stability in the gastrointestinal tract, these isolates were incubated in MRS broth of pH 6.5 (control), 3 and 2.5 and bile (oxgall) levels of 0% (control) 0.5% and 1% with aliquots plated on MRS

agar at 2, 4 and 24h. Aliquots of controls were analyzed by HPLC for D- and L-lactate. LAB with favorable stability and high L-lactate production were identified using fermentation kits (BioMerieux). **Results:** Ten bacteria were isolated from calf fecal samples. All were stable in bile at 0.5% and 1% and at pH 3 for up to 4h. Six isolates had favorable lactate profiles (L:D lactate ratio  $\leq 10$ ). These six isolates also had acceptable stability in bile (up to 24h in 1% oxgall bile) and acid (up to 4h in pH 3). Using the API system and various literature sources, the likely identities of the organisms were determined as *Lc lactis* subsp *cremoris*, *Lc raffinolactis*, *Lc lactis* subsp *lactis*, *Lc garviae*, *Lb ruminis* and *Lb alimentarius*. **Conclusion:** Six bacterial species may be potential candidates as probiotics for treating diarrhea with D-lactic acidosis in calves. Nevertheless, further research needs to be carried out to determine the in vivo stability, physiological and/or pharmacological impact of these bacteria. **Acknowledgements:** Funding for this project was provided by the Merck Company Foundation National Summer Student Research Program to RO and the NSERC Discovery Grants Program.

### 38 IN VITRO TRANSMEMBRANE PERMEATION OF SUNSCREEN OXYBENZONE AND ANALGESIC IBUPROFEN

*Jennifer Gambrel*, Xiaochen Gu; Faculty of Pharmacy, University of Manitoba, Winnipeg, Manitoba, Canada

**Purpose:** Oxybenzone is an essential UVA absorbent found in most commercial sunscreens and ibuprofen is a common analgesic that can be applied as a topical medication. The objective of this study was to evaluate the transmembrane permeation profiles of the two compounds when they were applied concurrently in vitro. **Methods:** In vitro diffusion studies were carried out at 37°C and 45°C, using Franz-style cells with artificial poly (dimethylsiloxane) (PDMS) membrane. A series of oxybenzone and ibuprofen samples with various concentrations (oxybenzone 0.1-1%, ibuprofen 1-5%) were applied to the donor compartments, either separately or in combination. Samples were collected from the receptor compartments at pre-determined time points for 6 hours. Concentrations of oxybenzone and ibuprofen were analyzed by a validated HPLC assay. **Results:** Oxybenzone and ibuprofen permeated across the PDMS membrane in all diffusion studies. When applied separately, overall permeation percentage at varying concentrations and temperatures was 4.92-29.56% for oxybenzone and 0.73-4.82% for ibuprofen respectively. When applied in combination, overall permeation percentage at varying concentrations and temperatures was 3.80-29.30% for oxybenzone and 0.26-1.76% for ibuprofen respectively. A reduced permeation was observed between oxybenzone and ibuprofen when both compounds were present concurrently, indicating potential interaction between the compounds in transmembrane profiles. The maximum permeation percentage was 29.56% for

oxybenzone at 0.1% and 45°C, and 4.82% for ibuprofen at 1% and 37°C respectively. Higher temperature did promote the diffusion process in terms of transmembrane permeation; however, there was no significant difference in permeation percentage between the two test temperatures. **Conclusions:** There was an interaction between sunscreen oxybenzone and analgesic ibuprofen across the PDMS membrane when they were present simultaneously. The potential transdermal interaction and systemic absorption from concurrent application of sunscreens and topical analgesics thus requires further systematic evaluation. **Acknowledgement:** The authors thank the financial support from the Merck Company Foundation National Summer Student Research Program.

### 39 IN VITRO AND IN VIVO PERCUTANEOUS PERMEATION OF INSECT REPELLENT N, N-DIETHYL-M-TOLUAMIDE (DEET) AND SUNSCREEN OXYBENZONE

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**Purpose:** The objective of this study was to investigate concurrent skin absorption of the insect repellent DEET and the sunscreen oxybenzone in vitro and in vivo. **Methods:** In vitro diffusion studies were carried out at 45°C, using Franz-style cells with piglet epidermis (300-500µm) as membrane model. DEET and oxybenzone at 5 mg/mL in 50% ethanol (E), polyethylene glycol 400 (PEG-400) and propylene glycol (PG) were used either separately or in combination for the evaluation. Three commercially available repellent and sunscreen products (Coppertone® Sunblock Lotion, OFF!® Repellent Lotion and OFF!® Repellent Lotion with Sunscreen) were applied to the back of six piglets for preliminary in vivo investigation. Tape strippings were collected at 2, 12 and 48 hours after the application. Concentrations of DEET and oxybenzone were analyzed using a validated HPLC assay. **Results:** Overall in vitro permeation ranged 0.6-18% for DEET and 0.4-20% for oxybenzone respectively. Enhanced permeation increase across piglet skin was found for both DEET and oxybenzone when the two compounds were present concurrently (DEET: 289% in PG, 243% in E and 112% in PEG-400; oxybenzone: 139% in PEG-400, 120% in PG and 112% in E). E and PG significantly increased the permeation of DEET across the membrane. Recovery of DEET and oxybenzone from in vivo tape stripping varied dependent upon sampling time and formulation applied. Overall recovery amounts at 48 hours were 5.3% for DEET and 22.4% for oxybenzone respectively. Combined formulation showed higher recovery of 81.8% for DEET and 135.0% for oxybenzone respectively compared to single-component counterpart at 48 hours. **Conclusions:** Permeation of the insect repellent DEET and sunscreen oxybenzone was synergistically enhanced when they were applied simultaneously

in vitro and in vivo. Mechanisms of such absorption synergy as well as approaches to reduce overall permeation of DEET and oxybenzone need to be systematically identified.

### 40 STUDY ON THE CORRELATION OF DRUG DISSOLUTION AND POLYMER SWELLING FROM A MATRIX TABLET USING TEXTURE ANALYZER

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**PURPOSE:** To study the relationship between drug dissolution and polymer swelling from a controlled release matrix tablet of pseudoephedrine using texture analyzer. **METHODS:** A series of controlled release matrix tablets of pseudoephedrine were prepared by direct compression method using identical compression force. Controlled release of pseudoephedrine was achieved by combined use of matrix excipients Compritol® 888 ATO (C) and Polyox® WSR 301 (P). Dissolution profiles of the tablets were evaluated using USP Method II. Thickness of gel formation and area under the curve (AUC, product of the force the probe sensed and the distance the probe traveled) during drug dissolution were also recorded using a Texture Analyzer. The relationship between drug dissolution and polymer swelling was correlated and interpreted. **RESULTS:** Drug dissolution within the first 90 minutes reduced with the increased proportion of C and P in tablet formulation. However, drug dissolution completed in 6 hours due to the aqueous solubility of pseudoephedrine. Thickness of gel formation as well as the AUC increased linearly with the dissolution time, indicating first-order kinetics of water penetration into tablet matrix. Linear correlation was also observed between thickness of gel formation and square of drug release percentage. Various dissolution parameters are listed in the following table. **CONCLUSIONS:** There was a linear relationship between drug dissolution and polymer swelling of a controlled release matrix tablet of pseudoephedrine. The study demonstrated a unique application of Texture Analyzer in characterization of tablet quality control and drug dissolution.

Formulation	C/P Content (w/w %)	Diffusional Exponent (n)	Release Rate Constant (k)	Correlation Coefficient (r <sup>2</sup> )	Dissolution Time (50%)
F1	3/10	0.439	0.084	0.995	0.92 hr
F2	3/15	0.470	0.073	0.996	1.00 hr
F3	3/20	0.504	0.061	0.996	1.14 hr
F4	3/25	0.500	0.057	0.995	1.27 hr
F5	3/30	0.526	0.049	0.996	1.38 hr
F6	3/50	0.498	0.052	0.998	1.65 hr

### 41 IN VITRO PERCUTANEOUS CHARACTERIZATION FROM CONCURRENT APPLICATION OF INSECT REPELLENTS AND SUNSCREENS

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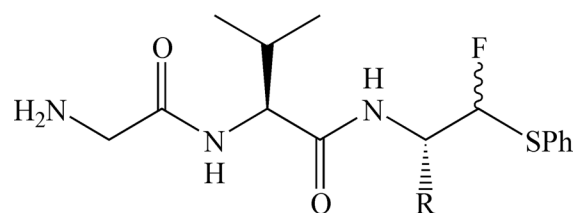
**Purpose:** To investigate the percutaneous characterization from concurrent application of commercially available insect repellents and sunscreens in vitro. **Methods:** Coppertone® Sunblock Lotion (P1), OFF® Skintastic Lotion (P2) and OFF® Skintastic Spray (P3) were tested, either individually or in combination at various application sequences or proportions. In vitro diffusion studies were carried out at 37°C, using Franz-style cells with piglet skin (300-500µm in thickness) as membrane model. Samples were collected hourly for 6 hours, and concentrations of the repellent DEET and the sunscreen oxybenzone were analyzed using a validated HPLC method. **Results:** Accumulated percutaneous permeation of both DEET and oxybenzone increased when insect repellent and sunscreen were applied simultaneously. Compared to individual P2 and P3, permeation of DEET increased 176% and 290% in P2+P1 and P3+P1, respectively. Compared to individual P1, permeation of oxybenzone increased 87% and 29% in P1+P2 and P1+P3, respectively. Compared to P1+P3, permeation increase of DEET and oxybenzone in P1+P2 was 255% and 32%, respectively. Permeation of oxybenzone when P1 was applied on top of P3 was 1.4 times higher than that when P3 was applied on top of P1, while permeation of DEET when P1 was applied on top of P3 was 1.9 times higher than that from individual P3. P1+P3 at 2:1 ratio produced 65% increase in DEET permeation but 63% decrease in oxybenzone permeation compared to P1+P3 at 1:2 ratio. Permeation of DEET from P1+P3 (2:1) and P1+P3 (1:2) increased by 316% and 153% respectively, compared to individual P3. **Conclusions:** Concurrent application of commercial insect repellent and sunscreen products resulted in synergistic percutaneous permeation of the repellent DEET and the sunscreen oxybenzone. The penetration profiles were dependent upon the type of formulations, application sequence and application proportion. Further studies are therefore needed to identify the mechanisms of such absorption synergy.

#### 42 FLUROPEPTIDOMIMETICS: A NOVEL DESIGN STRATEGY TO INHIBIT PROTEASES

Subhash C. Annedi, Kanchana Majumder, Sheeba Samson and *Lakshmi Kotra*; Leslie Dan Faculty of Pharmacy, Molecular Design and Information Technology Center; Department of Chemistry, University of Toronto, Toronto, Ontario, Canada

**Purpose:** Novel strategies to inhibit proteases are explored to design small molecule protease inhibitors as therapeutic agents. **Methods:** These compounds are designed as a novel class of mechanism-based inhibitors to mimic the transition-state of an oxyanion species during the hydrolysis of a peptide bond by a serine protease. Fluoro moiety is used to mimic the oxyanion and a series of inhibitors **1-5** were designed, synthesized and evaluated their inhibitory activity against chymotrypsin. The design of inhibitors incorporated the fluoropeptidomimetics strategy, first proposed by our research group and the design

principles appropriate for inhibitors against chymotrypsin. **Results:** Compounds **1-5** were synthesized in five steps starting from appropriate amino acids and were evaluated for their activities against chymotrypsin. Compounds **1** and **2** showed up to 60% and 70% inhibition in a time-dependent enzyme assay at 2 hours, respectively. Compounds **3-5** did not show any significant inhibition in a time-dependent enzyme assays, up to 300 mM. **Conclusion:** Inhibition was dependent on the S1' substitution which plays a key role in the binding of ligands to the active site of chymotrypsin. Bulky and hydrophobic substitutions at P1' position such as compounds **1** and **2** resulted in enhanced inhibition of the activity of chymotrypsin. Synthesis of inhibitors **1-5** and biological activity evaluations against chymotrypsin and their aqueous stabilities will be presented.



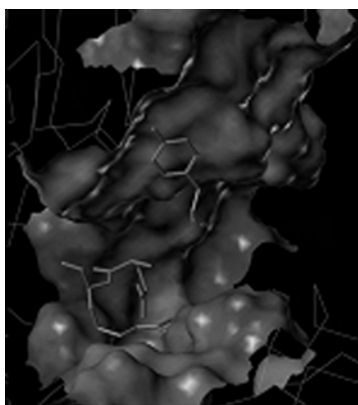
- 1** R = CH<sub>2</sub>Ph
- 2** R = CH<sub>2</sub>(Cyclohexyl)
- 3** R = CH(CH<sub>3</sub>)<sub>2</sub>
- 4** R = C(CH<sub>3</sub>)<sub>3</sub>
- 5** R = CH(CH<sub>3</sub>)C<sub>2</sub>H<sub>5</sub>

#### 43 DESIGN OF SMALL MOLECULE LIGANDS FOR INSULIN RECEPTOR – A 3D STRUCTURE-BASED STRATEGY

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**Purpose:** Design of novel small molecule ligands against insulin receptor using structure-based drug design strategies. **Methods:** The quaternary structure of the complex of insulin-insulin receptor was constructed using electron cryomicroscopy experiments and an atomic model was built by fitting the x-ray crystallographic structures of various domain substructures of the insulin receptor and that of insulin into the above EM struc-

ture (Ottensmeyer and coworkers, *Science*, 1999, 285, 1077). Based on the Electron microscopy images, explicit atomic model of insulin receptor (IR) binding with insulin was refined, including critical disulfide bonds building, and glycosylation sites. A geometry optimization on the new model was performed using molecular simulations package AMBER. This energy-minimized complex of IR binding with insulin along with several critical interactions between insulin and insulin receptor were used in the design of ligands. **Results:** Coupling the results of *in silico* chemical database search with core structures available in our laboratory, first set of compounds using hydantoin core were designed to mimic insulin binding, and their autophosphorylations were evaluated. **Conclusions:** For the first time, the three-dimensional model of insulin receptor was used and novel ligands were designed *de novo* to mimic interactions of insulin at its receptor. One of the compounds 4 could compete with insulin and inhibited up to 68% of IR autophosphorylation at 300 nM of 4 in 3T3IR cells induced by 1 nM insulin. This model can be effectively used to design potent insulin receptor ligands.



#### 44 A PRELIMINARY DESCRIPTION OF THE ROLE OF THE PRIMARY CARE PHARMACIST: AN ANALYSIS OF DRUG-RELATED PROBLEMS

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**Purpose:** A primary care pharmacist has multiple roles in an interdisciplinary team-based family practice setting. The aim of this study was to enhance our understanding of the features of the direct patient care role by analyzing pharmacist's initial medication assessments for patients who were referred by the members of the team. **Methods:** The initial pharmacist assessment was reviewed for patients referred to the pharmacist for comprehensive medication management over a 3-year period. Data was gathered from the pharmacy chart, pharmacist con-

sult notes, and medical chart (patient age, drug-related problems). Each drug-related problem (DRP) was described and characterized by considering the nature of the pharmacist's role and the nature of pharmacist-physician collaboration. From these findings, key aspects of the pharmacist's direct patient care role were identified. **Results:** 105 initial patient medication assessments were reviewed and 202 DRPs were identified (average of 1.9 DRPs/patient, range: 0 to 9 DRPs/patient). The most common issues included causes such as patient's gaps in medication knowledge (29.7%), need for additional therapy (22.3%), adverse drug reactions (16.8%), and drug interactions (6.4%). There was not a statistical difference observed in the number of DRP identified in patients who were greater and less than 65 years old. There were two types of approaches that were required from the pharmacist (a) proactive role (68.2%), (b) problem-solving (31.7%). The nature of the collaboration between the pharmacist and the patient was either shared care mode (48.5%) or more independent care role (51.5%). **Conclusions:** The findings revealed four features of pharmacist's role (a) identification of key functions (b) need for accessibility for patients of all ages, (c) integration within the team to allow for a proactive role, and (d) flexibility of pharmacist's involvement to allow for either shared care or independent patient care. Research conducted as part of the Merck Company Foundation National Summer Student Research Program 2003. *Poster has been submitted to the following conferences but results of the review process are pending Canadian Pharmacist Association Annual Meeting, Niagara-on-the Lake May 2004 and Canadian College of Clinical Pharmacy Annual Meeting, Winnipeg, June 2004.*

#### 45 THE INVOLVEMENT OF PXR IN HEPATIC GENE REGULATION DURING INFLAMMATION

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**Purpose.** Inflammation reduces the expression of numerous drug transporters and metabolizing enzymes. However, the mechanism of down-regulation is unknown. On the other hand, activation of the pregnane X receptor (PXR) induces many of these same genes. Hence, the purpose of this study was to determine if PXR is also involved in the regulation of drug transporters during inflammation. **Methods.** Wild-type (+/+) and PXR-null (-/-) mice were treated for 4 days with the PXR activators PCN or RU486. Another group of (+/+) and (-/-) mice were treated with LPS (5mg/kg), IL-6 (10,000U) or IL-1 $\beta$  (10,000U) for 6 hours. Reversal of induction was examined in PCN-treated (+/+) mice injected with LPS or IL-6 six hours prior to sacrifice. Levels of mRNA were measured from RNA isolated from the liver by real-time quantitative PCR using LightCycler<sup>®</sup> technology. **Results.** Treatment of (+/+) but not (-/-) mice with PCN or RU486 resulted in a significant induc-

tion in mRNA levels of *mdr1a*, *mrp2*, *mrp3*, *oatp2*, *bsep* and *cyp3a11*, confirming their regulation by PXR. The suppression of *mrp2* by LPS in (-/-) mice was significantly less than in (+/+ ) mice. LPS significantly decreased levels of *mrp3*, *oatp2*, *bsep*, *ntcp* and *mdr2* to similar extents in both (+/+) and (-/-) mice. The suppression of *mrp2*, *bsep* and *cyp3a11* by IL-6 seen in (+/+) mice was not seen in (-/-) mice. Transporter suppression by IL-1 $\beta$  was similar in both (+/+) and (-/-) mice. LPS and IL-6 treatments were found to suppress PCN-mediated induction of *pxr*, *mrp2*, *bsep* and *cyp3a11*. **Conclusions.** Our results suggest that PXR is involved in the mechanism of down-regulation of *mrp2* by LPS and in the reduction of *mrp2*, *bsep* and *cyp3a11* by IL-6 in mice. Hence, PXR levels may be an important factor in determining the expression of various drug transporters and drug metabolizing enzymes. Presented at the American Society for Clinical Pharmacology and Therapeutics Annual Meeting, March 24-27, 2004.

#### 46 COMPARISON OF ORAL INSULIN SPRAY VS S.C BOLUS IN PATIENTS WITH TYPE-1 DIABETES STABILIZED ON INSULIN PUMP (I.V. DRIP)

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**Introduction** The improvement in glucose control in diabetes mellitus is a major challenge for Type-1 on multiple daily injections. The RapidMist, a novel Diabetes Management System provide significantly improved needle-free, pain free, post-prandial glucose control, and allows insulin to be absorbed orally in the mouth. This system is based on a unique liquid aerosol formulation, which allows a precise insulin dose delivery directed in the mouth. **Purpose** The goal of this study was to evaluate the efficacy of the Oralin spray (10 puffs, no NPH) in Type-1 diabetic patients stabilized on insulin drip pump after a standard meal challenge at breakfast-time. **Method** In an open-label, randomized, crossover study, 11 Type-1 diabetic patients received Oralin spray via the RapidMist device or s.c injection (7-8 units) with a 360 cal Ensure liquid meal 15 minutes after each treatment. Table shows serum glucose and insulin levels after the dose of Oralin or s.c. injection at given time points.

#### Results

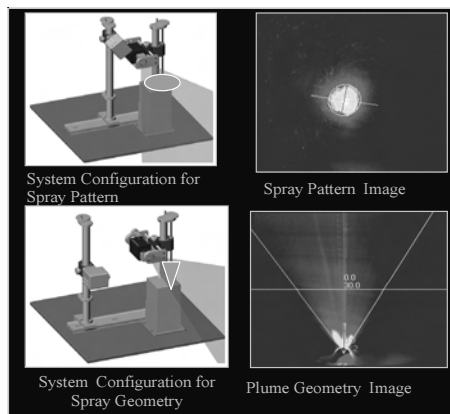
Time (mins)	Oralin Glucose	Bolus s.c. Glucose	Oralin Insulin	Bolus s.c. Insulin
0	105	98	26	19
15	94	120	68	20
60	125	200	39	34
120	179	283	26	26
240	160	193	17	24

**Conclusion** Oralin spray at mealtime controlled glucose levels in a comparable manner to s.c.-injected insulin. The onset action of Oralin was much faster and reached its peak level (Tmax) at 15 mins. The rise in serum insulin concentrations in the Oralin treated group was significantly higher compared to s.c. injection. Orally absorbed insulin (Oralin) proved to be effective in controlling meal related glucose excursion in Type-1 diabetics.

#### 47 LASER ILLUMINATED HIGH SPEED IMAGING FOR NASAL SPRAY PATTERN AND GEOMETRY ANALYSIS

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**Purpose:** To develop a High-Speed Imaging with Laser Illumination for nasal spray pattern and geometry analysis. **Method:** High-Speed Imaging with laser illumination is a fast and non-intrusive measurement technique to evaluate the performance characteristics of nasal spray pumps. An automated firing device using a predetermined set of actuation parameters such as force, acceleration and final velocity actuates the nasal spray pump. As the spray cuts across the laser sheet, light in the laser sheet is scattered by the droplets in the spray and captured by the camera. Spray pattern and spray geometry can be calculated from the pixel intensity of the resulting images captured by the camera. The actuation factors affecting the spray pattern and geometry measurements such as velocity of actuation, acceleration, force, hold time and return time have been studied as well. **Results:** The imaging technique has many advantages over the current TLC technique for spray pattern determination for nasal spray products. The imaging method is fast, less tedious to execute, more reproducible and less subjected to analyst's interpretation. The velocity of actuation was found to be the most important factor affecting the outcome of the measurements. **Conclusion:** High-Speed Imaging with Laser Illumination can be used as an alternative method for nasal spray pattern and geometry analysis.



#### 48 ACTIVITY OF HYPOXIS HEMEROCALLIDEA AND SUTHERLANDIA FRUTESCENS AGAINST CYTOCHROME P450 3A4-MEDIATED METABOLISM

Brian Foster, Mills, Edward, Arnason, John T, Ruddock, Patrick, Kearns, Nikia, Dillon, Jo-Anne R., Cameron, D. William, van Heeswijk, Rolf, Kanfer, Isadore; Centre for Research in Biopharmaceuticals and Biotechnology,

University of Ottawa; Therapeutic Products Directorate, Health Canada, Ottawa; Canadian College of Naturopathic Medicine, North York; Ottawa Hospital Research Institute, Ottawa, Ontario, Canada; and Rhodes University, Faculty of Pharmacy, Grahamstown, South Africa

**Purpose:** Research suggests that some Natural Health Products (NHPs) – drug interactions may affect biotransformation enzymes and transport proteins. In addition to potentially affecting the safety and efficacy of the drug or NHP, this interaction may act synergistically or antagonistically with antibiotics, which could lead to improved or adverse clinical outcomes. This study was undertaken to characterize the effect of *Hypoxis hemerocallidea* (HH), Moducare capsules, and *Sutherlandia frutescens* (SF) against *Neisseria gonorrhoeae* (NG) and *Enterococcus faecalis* (EF), cytochrome P450 3A4-mediated (CYP3A4) metabolism, and P-glycoprotein (Pgp) transport. **Methods:** Authenticated herbals samples and Moducare capsules were obtained from South Africa. The herbal samples were ground to a common consistency and capsules (5) were batched. HH was analyzed for hyposide content. Aqueous and methanol extracts (100 mg/ml) were prepared fresh and aliquots tested for their antimicrobial activity; and potential to affect ATPase activity associated with Pgp and human cytochrome P450 3A4-mediated metabolism determined using *in vitro* bioassays with the commercially available microsomes. **Results:** Our data indicates that methanolic extracts of SF had weak antibacterial activity against NG but not EF. HH, Moducare and SF extracts had a moderate inhibitory activity on CYP3A4. Aqueous extracts had a modest affect relative to verapamil on Pgp. **Conclusions:** These herbal products have pharmacological properties including the potential capacity to affect drug safety and efficacy. Further studies are warranted against a wider range of cytochrome P450 isozymes and to determine if these effects are clinically significant.

**49 THE EFFECT OF BERBERINE CONTAINING BOTANICALS ON CYTOCHROME P450-MEDIATED METABOLISM.** Scott, Ian M, Ruddick, Partick, Leduc, Rene, Dillon, Jo-Anne R., Arnason, John T. and Brian Foster; Centre for Research in Biopharmaceuticals and Biotechnol

gy, University of Ottawa; Therapeutic Products Directorate, Health Canada, Ottawa, Ontario, Canada

**Purpose:** Goldenseal *Hydrastis canadensis* (Ranunculaceae) is a popular herbal supplement for gastrointestinal ailments. It contains the alkaloids berberine and hydrastine, hydrastinine and canadine. Three other herbals, barberry *Berberis vulgaris*, Oregon grape *Mahonia aquifolium* and Goldenthead *Coptis groenlandica* also contain measurable amounts of these compounds and have a long ethnobotanical record in North

America. **Methods:** The potential for these four botanical species to affect human cytochrome P450 3A4, 2C19 and 19 mediated metabolism was determined using *in vitro* bioassays with the commercially available microsomes. Berberine, hydrastine, hydrastinine and canadine concentrations were determined by HPLC. **Results:** It was determined that 55% ethanolic extracts of *H. canadensis* were inhibitory to all three cytochrome P450 enzymes. *C. groenlandica* and *B. vulgaris* were less active but similar while *M. berberis* was the least inhibitory. HPLC analyses indicated that of the four species tested, *H. canadensis* has the highest concentration of the marker compounds. **Conclusions:** These botanicals have the potential to affect human drug and intermediary metabolism. This activity is independent of the concentration of the major biomarkers for these botanicals.

**50 COLLECTIVE PRESCRIPTION PROTOCOL FOR PROVISION OF MEFLOQUINE TO CANADIAN FORCES PERSONNEL DEPLOYING TO AFGHANISTAN**

Douglas Doucette, Shannon Sinclair, Dominique Gagnon, Régis Vaillancourt; Central Medical Equipment Depot Petawawa, Canadian Forces Base Petawawa, Ontario; Forward Medical Equipment Depot, Health Services Support Company, Canadian Contingent Task Force Kabul, Operation Athena, Kabul, Afghanistan; 5Field Ambulance, Canadian Forces Base Valcartier, Valcartier, Quebec; Directorate of Medical Policy, Pharmacy Policies and Standards, Canadian Forces Health Services, Ottawa, Ontario, Canada

**Purpose:** Canada's contribution to the United Nations (UN) authorized International Security Assistance Force (ISAF) in Kabul, Afghanistan, Op ATHENA, involved the preparation of 1900 military personnel from Canadian Forces Base (CFB) Petawawa in June 2003 and 1500 military personnel from CFB Valcartier in October 2003 for deployment. Local Pharmacy Officers were tasked to provide antimalarial medications to all personnel deploying. **Methods:** Major challenges identified were: ensuring all personnel were carefully screened for appropriate selection of an antimalarial, counseled on medication options for malaria prophylaxis, and received comprehensive information on this therapy; and preparing individual prescriptions for the antimalarial drug, mefloquine, without significant disruption of daily base pharmacy operations. Collective prescription protocol (CPP) was employed in Petawawa and Valcartier to delegate prescriptive authority to Pharmacy Officers and civilian pharmacists employed within the Department of National Defence. This poster will outline how the CPP was planned and implemented by pharmacists to protect the health of military personnel deployed to Afghanistan. **Results:** It will also discuss the enhanced visibility of the pharmacist as an integral health care provider to the target group. **Conclusion:** This

program successfully met its objectives and has been sanctioned by the Surgeon-General as a model for provision of medications to large numbers of personnel for future military deployments.

#### 51 DRUG UTILIZATION IN THE CANADIAN ARMED FORCES

Régis Vaillancourt, Eden d'Entremont, BSP, Alan Gervais, BSP, *Dave Cecillon*; Directorate of Medical Policy, Pharmacy Policy and Standards, Canadian Forces Health Services, Ottawa, Ontario, Canada

**Objective:** To describe drug utilization by members of the Canadian Forces (CF) and compare it to the Canadian civilian population. **Method:** CF procurement data for the 2002-2003 fiscal year was obtained from McKesson Canada to assess drug utilization in CF members. IMS Health Canada provided prescription data from Canadian retail pharmacies for the same period. Data from both was sorted into three reports: total cost of prescriptions according to therapeutic class, top 20 active ingredients by number, and top 20 active ingredients by value. It was then analyzed to compare drug usage among the military and civilian populations. **Results:** Drugs for cardiovascular disease are the most widely used agents followed by drugs for psychiatric disorders for both military personnel and civilians. The top 10 therapeutic classes are similar for both groups, although the order in which they appear does vary. OTC medications appear much more frequently among the most commonly used active ingredients by the military population. Cardiovascular medications represent eight of the top 20 expenditures by civilians, compared to four of the top 20 in the CF population. **Discussion:** Notable differences in drug usage exist between military personnel and the civilian population in the rate of OTC usage, expenditure on sildenafil and expenditure on psychiatric medications. These differences may be attributable to CF formulary restrictions as well as differences in population demographics and data collection.

#### 52 PICTOGRAPHIC INSTRUCTIONS FOR MEDICATIONS: DO OTHER CULTURES INTERPRET THEM CORRECTLY?

Régis Vaillancourt, Zahra Sadikali, John B. Collins, Rosemin Kassam; Directorate of Medical Policy, Pharmacy Policy and Standards, Directorate Canadian Forces Health Services, Ottawa, Ontario; University of British Columbia, Vancouver, British Columbia, Canada

**Background:** Dispensing medication is a major service provided by Canadian Forces humanitarian relief missions around the world—often in developing countries. This study tested a set of sixteen pre-developed pictograms to determine whether they accurately communicated the written directions found on medication labels to ethnic respondents who neither speak nor

read English, French or Spanish. **Objective:** (1) To determine whether ethnically diverse individuals could understand the pictogram meanings without additional aids such as verbal instructions or explanations, and (2) to identify appropriate modifications to the pictograms to reduce interpretation errors. **Method:** Both qualitative and quantitative methods evaluated the pictograms' interpretability among three ethnic groups; Cantonese, Somali and Punjabi. Standard ANOVAs tested for differences due to ethnicity and other demographics. Results: Only four of the 16 initial pictograms tested were interpreted correctly by 80% of participants. Relaxing the criterion from 80% to 50% included eight more. Modifications to problem icon elements further improved interpretation accuracy levels by 22% for a 'best-of-three' tally of 67.15%. Quantity errors were twice as common as timing, administration route or auxiliary instruction errors. **Conclusions:** Participants could identify particular pictographic symbols they found confusing or ambiguous. Basic education and time since immigration predicted interpretation accuracy better than ethnicity or any other demographic characteristic.

#### 53 PRE-TESTING OF PICTOGRAMS USED IN MEDICINES DISPENSED IN MISSIONS OF HUMANITARIAN RELIEF

Régis Vaillancourt, Directorate of Medical Policy, Pharmacy Policy and Standards, Canadian Forces Health Services, Ottawa, Ontario, Canada; Kath Ryan, Gordon Becket, Sulakshi de Silva; School of Pharmacy, University of Otago, New Zealand

**Rationale:** The Canadian Forces Disaster Assistance Response Team (DART) provides health services during humanitarian relief missions. The recipients of health care during these deployments often do not speak English, French, or Spanish; many are also illiterate. This presents serious problems for communicating medication use. **Objectives:** To assess the effectiveness and comprehensibility of medication label pictograms among non-English speaking people. To determine the cultural appropriateness of the images used in such pictograms. **Study Design:** For each of three different ethnic populations, a focus group was convened. Each focus group consisted of 6-8 participants with a diverse range of education, literacy, and occupations. Discussion was facilitated by and interpreter and individual interviews were used to determine responses to each pictogram. **Results:** Some pictograms were understood by all ethnic groups. Other must be redesigned to either address cultural values or allow greater comprehension. **Importance:** The findings will help to create pictograms, which are suitable for general use in non-English populations. These universal pictograms will help to enhance the provision of health care during humanitarian missions.

**54 SYMPTOM RESOLUTION OF COMMON AILMENTS TREATED WITH OVER-THE-COUNTER MEDICATIONS PROVIDED DIRECTLY BY COMMUNITY PHARMACISTS**

Régis Vaillancourt, Mark Kearney, Michel Trottier, Janice Ma, Alan Gervais; BSP, Directorate of Medical Policy, Pharmacy Policy and Standards, Canadian Forces, Ottawa, Ontario; Rosemin Kassam, University of British Columbia, Vancouver, British Columbia, Canada

**Rationale:** In an earlier pilot project, patients were provided with an information card that enabled them to obtain non-prescription, over-the-counter (OTC) medications directly from a community pharmacist. However, because OTC medications may be limited in their efficacy, symptom resolution may be suboptimal, or may vary according to the condition treated. A sub-analysis of the data was thus performed to determine the effectiveness of eligible OTC products in resolving symptoms for minor common ailments. **Objective:** To determine if the effectiveness of symptom resolution varied among therapeutic classes of OTC medications obtained directly from a pharmacist. **Methods:** Patients who obtained an eligible OTC medication were contacted within 8 weeks to participate in a telephone survey. Survey results were analyzed to determine treatment outcomes as reported by the patients. Results were grouped in four drug classes: analgesics; antihistamines; cough and cold; and other. **Results:** Between May 1, 2002 and March 31, 2003, 334 OTC medications were dispensed during 263 direct encounters with a community pharmacist. Overall, patients reported complete resolution, partial resolution and no improvement of their symptoms 84%, 15% and 1% of the time, respectively; no patients reported worsening of their symptoms with OTC treatment. Similar results were observed among the four different drug classes. **Conclusion:** Patients experienced a high rate of symptom resolution, regardless of the type of ailment being treated. OTC medications, provided directly by a community pharmacist, are effective in relieving symptoms of common ailments in most patients.

**55 THE EFFECTS OF MEDICATION USE ON THE RISK OF ACCIDENTS AMONG MEMBERS OF THE CANADIAN FORCES**

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**Rationale:** Most epidemiological studies that evaluate the impact of medications on risk of accidents have focused on elderly patients and benzodiazepines. This study has been performed to assess accident risk and medication use among a population of younger adults. **Objectives:** To determine if spe-

cific classes of medication are more likely to be consumed during the two weeks prior to an accident in a general adult population. **Methods:** A database was constructed to link information about accidents and medication use Canadian Forces members between January 1999 and December 2001. The case period was defined as the two weeks prior to accident occurrence. In the first analysis, an accident-free historical control period was defined for each subject and medication use compared between case and control periods using incidence risk ratio. A second analysis was then performed using an accident-free control matched for age, sex, occupation, and employment date, to yield an odds ratio for each class of medication. **Results:** Significantly, increased odds ratios were detected for 12 different medication classes. Clinically significant odds ratios were observed for antispasmodics and anticholinergics (OR 5.598), estrogens (OR 2.777), and digestives (OR 3.256). Odds ratios for the remaining drug categories ranged from 1.254 (for laxatives) to 1.795 (for beta-blockers). **Conclusion:** This analysis identified several medications that were more likely to have been taken in the two weeks prior to an accident. Further studies should be undertaken to confirm the magnitude of risk associated with these drugs.

**56 USE OF GASTRIC ACID SUPPRESSANTS AMONG USERS OF ANTIDEPRESSANTS IN THE CANADIAN FORCES**

Régis Vaillancourt, Janice Ma; Pharmacy Policy and Standards, Canadian Forces Health Services, Ottawa, Ontario; J.Sampalis, JSS Medical Research Inc; Montréal, Quebec, Canada

**Rationale:** In vitro studies and database analyses suggest that gastric bleeding may be increased due to antiplatelet effects from serotonin reuptake inhibitors. However, antidepressants can cause other gastrointestinal effects for which suppressants of gastric acid (SGA) are prescribed. To date, there is no information to describe SGA use overall following antidepressant prescribing in a general adult population. **Objectives:** To determine if prescribing of SGA increases upon initiation of antidepressant therapy, and to compare usage rates of SGA among the different antidepressant classes. **Methods:** A retrospective analysis was performed of pharmacy records from Canadian Forces members who received any antidepressant (excluding bupropion for smoking cessation) between 1998 and 2002. Relative risk of use of SGA prior to and after initiation of antidepressants was calculated using McNemar's test for matched pairs. Logistic regression analysis was used to assess the effects of gastric irritants and demographic factors upon SGA use. A case-control analysis was also performed to compare SGA usage among users of salbutamol as compared to users of antidepressants. **Results:** A total 5588 members were identified from our database, representing 8722 discrete exposures to antidepressants. SGA were prescribed in approximately 20% of anti-

depressant users. NSAIDs were the gastric irritant medications most commonly used (43% of antidepressant users). Preliminary analysis of the results suggests that SGA are not more likely to be prescribed following initiation of an antidepressant. **Conclusion:** The prescribing of gastric acid suppressants does not appear to increase following initiation of antidepressant therapy among non-elderly adults.

#### 57 DEVELOPMENT OF PATHOLOGICAL CUTANEOUS SUBSTITUTES BY TISSUE ENGINEERING TECHNIQUES FOR DERMOPHARMACEUTICAL APPLICATIONS

Marc Lapointe, Auger, François, Pouliot, Roxane; Faculté de Pharmacie; Département de Chirurgie, Faculté de Médecine; Laboratoire d'Organogénèse Expérimentale, Hôpital St-Sacrement du Centre Hospitalier Affilié (CHA) à l'Université Laval, Ste-Foy, Québec, Canada

**Purpose.** Psoriasis is a chronic skin disease characterized by a thickening and disorganisation of the skin's protective barrier, or *stratum corneum*. The pathology seems to be derived from the early expression of enzymes during the differentiation process of keratinocyte cells. More specifically, the transglutaminase enzymes, which are responsible for covalently linking proteins in the formation of the *stratum corneum*. Psoriasis affects millions of people worldwide and there is no definitive cure. **Methods.** With the help of tissue engineering techniques, particularly the auto-assembly method, to produce psoriatic and healthy cutaneous substitutes, it will be possible to shed light on the roles of specific enzymes linked to psoriasis, including transglutaminases. **Results.** Preliminary results show that the cutaneous substitutes produced through tissue engineering are macroscopically similar to psoriatic skin. We noticed whiter and thicker substitutes when using psoriatic cells, which correspond to an accumulation of dead cells on the surface due to the acceleration of cellular division, also observed in psoriasis. In addition, the expression of transglutaminase in these substitutes appears earlier than in those produced with healthy cells. Mason's trichrome staining of slices of psoriatic substitutes has showed a thickening of the *stratum corneum* (hyperkeratosis) as well as a loss of the granular layer (agranulosis). **Conclusion.** The observations made from psoriatic skin substitutes produced by tissue engineering concur with the observations made from psoriatic lesions found on patients.

#### 58 EFFECT OF THE GASTROINTESTINAL ENVIRONMENT ON PURECELL COMPLEX (PCT) AND EVALUATION OF ITS ABSORPTION.

JF Mercier, Roxane Pouliot, JF Cloutier; Faculty of Pharmacy, University Laval; PureCell Technologies Inc., Quebec City, Quebec, Canada

**Purpose:** The goal of our research was to determine the effect of the gastrointestinal environment on the photoactivity of PureCell Complex (PCT) corresponding to thylakoid membrane extracts from plants, and to quantify its intestinal absorption. **Methods:** The PCT is composed of proteins, lipids and pigments and its three-dimensional structure gives to the latter its antioxidant and anti-inflammatory properties. We tested *in vitro* different enzymes like protease, lipase, invertase, amylase, peptidase and trypsin at various concentrations. We use fluorescence spectroscopy to determine their effect on PCT photoactivity. To quantify the absorption of PCT by the intestinal membrane, we selected the everted rat gut sac as technique. The relative concentration of PCT and its pigments was quantified by the absorbance of light from 400nm to 800nm. **Results:** We found that the buffering conditions and the enzymes tested, lowered the photoactivity of the PCT. At the lowest concentration 0.01U, protease, lipase, and amylase have inhibited the photochemistry of PCT. The enzymes invertase (3U) and trypsin inhibited the fluorescence of PCT. The peptidase from 0.01U to 3U did not inhibit the fluorescence of PCT meaning that the PCT has conserved its photochemical action. We found that the intestinal membrane absorb PCT but to a relatively low extent. We found some binding selectivity of PCT to intestinal location such as duodenum, jejunum or colon. We found that the duodenum had in average 94.5 % of PCT on the outside, 7.21% on the membrane and 0.08% that cross the membrane. Jejunum had 92.7 % of PCT outside, 3.13% on the membrane, and 0.04% inside. The colon had 97.3 % outside, 2.74% on the membrane and 0.01% inside. **Conclusions:** The PCT seems to be sensitive to the environment of the gastrointestinal tract and its absorption by the intestinal membrane was low in the everted gut sac model using pigments fluorescence as markers. However, we recently observed that the anti-inflammatory properties of PCT was not affected by the gastrointestinal environment suggesting that fluorescence spectroscopy is not suitable to measure and correlate PCT presence with its inflammatory activity. More extensive studies with other markers will be suitable. The actual study shows that the external binding of PCT was high and makes it a potential new drug candidate to prevent or treat local inflammatory bowel diseases. **Acknowledgements:** This research was made possible by PureCell Technologies inc., the Faculty of pharmacy of Université Laval and by the Merck Company Foundation National Summer Student Research Program.

#### 59 SOLUBILIZATION OF POORLY-WATER SOLUBLE DRUGS USING HYDROXYPROPYLCELLULOSE-G-POLY (ETHYLENE GLYCOL) CETYL ETHER POLYMERIC MICELLES FOR ORAL DELIVERY

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**Purpose.** To exploit the solubilizing potential of hydroxypropylcellulose-*g*-poly (ethyleneglycol) cetyl ether (HPC-*g*-PEG-C<sub>16</sub>) polymeric micelles towards poorly-water soluble drugs in order to improve their oral bioavailability.

**Methods.** Hydrophobically-modified HPC-*g*-PEG-C<sub>16</sub> graft copolymer was synthesized by attaching hydrophobic hexadecyl residues to the hydrophilic HPC backbone *via* short PEG linkers. Cyclosporin A (CsA), a highly effective immunosuppressant, was selected as model drug. Its water solubility is as low as 23 $\mu$ g/mL. CsA-loaded HPC-*g*-PEG-C<sub>16</sub> micelles were prepared by a dialysis procedure using initial CsA loadings of 2.5-40% (*w/w*). Incorporated CsA was assayed by HPLC at 210 nm. The cytotoxicity of HPC, PEG-C<sub>16</sub> and HPC-*g*-PEG-C<sub>16</sub> towards the human colon adenocarcinoma, Caco-2, cells was evaluated using the MTT colorimetric assay. Transport of free CsA or micelles-loaded CsA across Caco-2 monolayers was evaluated at predetermined time points. Pluronic P85<sup>®</sup> polymer was added as P-glycoprotein inhibitor. **Results.** At 25% (*w/w*) of initially added CsA, HPC-*g*-PEG-C<sub>16</sub> micelles showed 22% entrapment efficiency for CsA, compared to 4% in the case of free HPC polymer. After 24 h, free HPC showed no cytotoxicity while free PEG-C<sub>16</sub> inhibited cell growth even at low concentrations. Most importantly, the study revealed that HPC-*g*-PEG-C<sub>16</sub> exhibited no significant cytotoxicity at a concentration as high as 10 g/L. Following 240 min of transport, the apical to basal permeability of CsA across caco-2 cells increased by 3 times when loaded in HPC-*g*-PEG-C<sub>16</sub>, compared to free CsA. **Conclusions.** HPC-*g*-PEG-C<sub>16</sub> polymeric micelles increased the aqueous solubility of the lipophilic drug CsA. Their very low cytotoxicity and high permeability represent promising characteristics for the development of a novel polymeric drug carrier for the oral delivery of poorly-water soluble drugs. NSERC and Rx&D are acknowledged for financial support. This work has been presented at the 2003 AAPS annual meeting on October 30 and received the 2003 Award of the "Pharmaceutics and Drug Delivery" section.

#### 60 TEXTURE PROFILE ANALYSIS AS A MEAN TO ASSESS THE MECHANICAL PROPERTIES OF THERMOREVERSIBLE MUCOADHESIVE HYDROGELS

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**Purpose.** Based on the assessment of mechanical properties, the purpose of the current study is to select the optimum thermoreversible mucoadhesive hydrogel formulation, aimed to overcome the drawbacks of conventional nasal dosage forms such as poor residence time, leakage or difficulty of application. **Methods.** Aqueous solutions, of different concentrations of thermoreversible polymers poloxamer407 (P407) and poloxamer188 (P188) with or without the mucoadhesive polymers carbopol 934P (CP934P) or polycarbophil (PC), were

prepared. Their gelation temperatures were determined using the inverting test method. Kept at 34°C $\pm$ 0.5 for 30 minutes prior testing, three replicates from each free flowing liquid formulation were allowed to form gels. Texture profile analysis (TPA) was then performed using the texture analyser TA-XT2i (Texture Technologies Corp. NY) where 2cm diameter cylindrical acrylic probe was twice compressed into each formulation at 34°C to 5.0mm depth, at pre-test speed of 5.0mm/s, test and post-test speed of 1.0mm/s, and recovery period of 15s between the 2 compression cycles. From the resultant force-time curve, values of hardness, adhesiveness and cohesiveness were determined. Results were analysed using artificial neural networks. **Results.** Formulation with optimum mechanical properties appeared to be that containing P407/P188/PC of concentrations 15.0/25.0/0.1 (%w/w) where the values of hardness, adhesiveness, and cohesiveness were 2.03 N, 7.20 Nmm, 1.06 Nmm respectively. These properties were negligible for formulations not converted into gels at body temperature. PC proved to play a considerable role in cohesiveness (relative importance 83%, R<sup>2</sup> 0.946 and MSE 0,001). Cohesiveness, when weak, affects the adhesiveness. **Conclusion.** TPA, a simple and rapid procedure, is valuable in the scanning of the mechanical characteristics of different thermoreversible hydrogel formulations to obtain the suitable candidate for mucosal application.

#### 61 CHARACTERIZATION OF RECOMBINANT AMINOPEPTIDASE P

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**Introduction** To better understand the role of the metallopeptidase X-prolyl aminopeptidase (APP) in angiotensin I-converting enzyme inhibitors (ACEi) side effects, our laboratory used recombinant technology to produce human APP enzyme. The purpose of this study is to characterize the catalytic properties of this recombinant enzyme using different experimental conditions, and to compare these values to known data published elsewhere. **Materials & methods** Recombinant metallopeptidase catalytic activities and characteristics were assessed using various methods, namely time-point spectrofluorometry and HPLC techniques. For this, synthetic, natural and novel internally quenched fluorescent substrates were studied, and their catalytic properties ( $k_{cat}$ ,  $K_m$ ) determined. Optimal pH ranges for recombinant APP activity, as well as metal ion requirements were assessed. The inhibition profile of the recombinant enzyme was studied using the newly developed fluorescent substrate (IC50,  $K_i$ ). **Results** Optimal pH conditions determined for the recombinant enzyme closely matched those of an enzyme preparation purified from animal tissues (rat, bovine & porcine) previously published. Affinity constants of the recombinant form for its physiological



substrates (bradykinin and its carboxy-terminal truncated active metabolite, des-Arg<sup>9</sup>-BK) are very interesting and the IC50 values calculated for each ACEi opens new area of research on the pathophysiology of ACEi associated AO. Newly developed internally quenched fluorescent substrates were also characterized. The results obtained have been included in a manuscript, which has been submitted to a peer-reviewed journal. **Conclusions** These results are the first obtained evaluating a recombinant form of human aminopeptidase P, its activity and inhibition profile. This study is the basis for further studies for the study of variant forms of the enzyme, and the eventual design of a screening test to detect patient susceptibility to develop acute-side effects when treated with an ACEi. **Acknowledgements** Funding for this project was provided by the Merck Company Foundation National Summer Student Research Fund (Yvan Bao Loc Tran), and by the CIHR (G Molinaro, B Pharm, PhD candidate, and Professor A Adam).

#### 62 DETERMINATION OF RESIDUAL GLUTARALDEHYDE ON SOLID SURFACES AFTER SIMULATING THE DISINFECTANT FOGGING OF A PHARMACEUTICAL ASEPTIC ROOM

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**Purpose:** For several years, glutaraldehyde based fogging solution was used in disinfecting aseptic facilities. Although the levels of air-borne glutaraldehyde after fogging inside an aseptic room and its decay with time have been investigated, the residual levels of glutaraldehyde on solid surfaces has never been clearly established. **Method:** In this study, different surfaces were intentionally contaminated with glutaraldehyde to simulate potential contamination of solid surfaces after fogging of a pharmaceutical aseptic room. A gradient HPLC method with UV detection after derivatization with the chromophore 2,4-dinitrophenylhydrazine, was employed to measure levels of residual glutaraldehyde on solid surfaces. Swabs made of different swabbing materials such as polyurethane foam or polyesters were used to sample the surfaces. **Results:** The linearity of the HPLC method has been established at concentrations ranging from 0.003mg/mL to 1.25mg/mL with a correlation coefficient of 0.9996 and the detection limit has been established at 0.001mg/mL. This detection limit represents 1/10 of the strictest Subject Exposure Limit (SEL) available. Nearly 100% of glutaraldehyde was initially recovered 4 hours after solid surface contamination. However, the level of glutaraldehyde measured tends to decrease significantly over a period of 72 hours. **Conclusion:** Glutaraldehyde is very difficult to recover from swabbing with solvents and extensive washing of the contaminated surface is necessary. Oxidation of glutaraldehyde upon exposure to ambient air could certainly explain the decrease observed in the contamination levels with time. Therefore, ac-

cumulation of glutaraldehyde on a solid surface appears unlikely. Nevertheless, toxicity issues with the handling of glutaraldehyde have motivated its replacement with alternative germicides.

#### 63 COMPARISON OF CROSSLINKING METHODS TO FORM CHITOSAN BASED DRUG DELIVERY AND TISSUE ENGINEERING MATRICES

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**Purpose** Entrapment of bioactive molecules, such as enzymes, drugs, vitamins, and peptides, in stabilizing matrices are desired by the pharmaceutical and biomedical industry for drug delivery and tissue engineering. Over the past decade, the biopolymer chitosan has attracted interest as a potential matrix for immobilization or controlled release of cells and numerous bioactive compounds because of it is biocompatible and bioactive. However, typical methods of matrix formation and molecule entrapment have included toxic cross-linking agents, or resulted in less than optimal entrapment or material properties. We investigated new methods of molecule entrapment and matrix formation with the goal of developing optimal chitosan matrices for drug delivery and tissue engineering. **Methods** Medical grade chitosan was used to make gels of varying degree of deacetylation, molecular weight, and concentration. These gels were treated with cross-linking agents (TPP, glutaraldehyde, EDC, DTBP), and then processed in different forms (wet gel, dried or lyophilized). Properties of the matrix that are important to drug delivery and tissue engineering were then tested, these included pore size distribution, cross-linking density, water permeability, tensile properties, attachment and retention of biomarker molecule, and matrix degradation. **Results** Both EDC and DTBP were found to be very promising cross-linking agents for chitosan. EDC was found to effectively immobilize bimolecular to the chitosan matrix. DTBP cross linked the chitosan polymer to form matrices with superior strength characteristics compared to the traditional cross linker glutaraldehyde, while retaining its optima pore size distribution and permeability properties. **Conclusions** New methods of forming chitosan matrices for drug delivery and tissue engineering have been developed, and further optimization of these methods for specific applications is very promising.

#### 64 A FEASIBILITY STUDY TO DEVELOP HPLC ASSAY FOR NUCLEOSIDE ANTI-CANCER AGENTS FOR PHARMACOKINETIC STUDIES

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**Purpose:** To develop sensitive and specific HPLC assay for cladribine in plasma for pharmacokinetic studies in humans and

animal models. **Method:** A Medline (Pubmed) search from 1993 and onward was conducted to review the current HPLC assays available for measurement of nucleoside anti-cancer agents in biological samples. Keywords such as HPLC, pharmacokinetics, cancer, nucleosides, and therapy were used. **Results:** Several assay methods based on HPLC have been reported. These include use of reversed phase chromatography and ion-paired chromatography for separation. Detection was performed by mass spectrometer with electrospray ionization or ultraviolet (UV) detector. Extraction of nucleoside anticancer agents was performed using deproteinization using perchloric acid, on-line HPLC sample cleanup, or off-line using solid phase extraction (SPE) technique. Based on this information, we propose to develop a Standard Operating Protocol for cladribine. This method would include a C18 reversed phase column (250 x 2 mm id) preceded by a guard column using similar packing and stationary phase material. The mobile phase would include a phosphate buffer with a suitable organic modifier such as acetonitrile and/or methanol. Detection would be made by UV detector set at wavelength of 265 nm and sensitivity at 0.01 AUF. The system would be operated isocratically at room temperature. A C8 SPE (100 mg packing material) would be used for extracting the nucleoside anti-cancer drugs from plasma following standard procedure with ethylacetate as the desorbing solvent. **Conclusions:** HPLC with UV detection appears to be a suitable method with sufficient sensitivity and specificity to quantify cladribine and other nucleoside analogues in plasma for pharmacokinetics studies. **Acknowledgements:** Funding for this project was provided in part by the Merck Co. Foundation Summer Research Program

#### 65 EFFECT OF DILTIAZEM ON THE HEMODYNAMIC RESPONSE TO ADENOSINE *IN VIVO*

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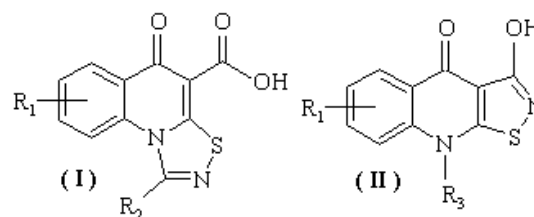
**Purpose:** To determine the effect of diltiazem on the hemodynamic response to adenosine using an *in vivo* rabbit model. **Methods:** Male New Zealand white rabbits (n = 6) weighing between 4 - 6 kg will be used. Each rabbit will receive diltiazem (Biovail Corp, Mississauga, Ont. Canada) 5 mg/kg s.c. bid for five doses. A separate group of animals (n = 7) will be used as control. On the day of experiment, a modified butterfly catheter with a 21G 3/4 in needle (E-Z set®, Deseret Medical Inc., Becton Dickinson) was inserted into a central ear artery for hemodynamic recording, and an unmodified butterfly catheter into a marginal vein for infusion. Adenosine (Sigma Chem Co.) was given to each rabbit by constant iv infusion at 200 :g/kg and 500 :g/kg over a 10-min period. A washout period of two hrs between each infusion was used to allow haemodynamic variables returning to pre-treatment levels. BP

and HR were determined continuously during the infusion, and for 20 min after the infusion. **Results:** Diltiazem decreased MAP from 76 ! 8 to 62 ! 6 mm Hg, but had no effect on HR. In the diltiazem treated rabbits, adenosine (200 :g/kg) decreased MAP from 62 ! 6 to 56 ! 5 mm Hg at the end of infusion (10 min). HR was increased from 239 ! 27 to 251 ! 33 bpm during infusion. At the higher dose (500 :g/kg), adenosine decreased MAP from 62 ! 5 to 50 ! 12 mm Hg, and increased HR from 250 ! 40 to 266 ! 33 bpm. **Conclusion:** Hemodynamic effects of adenosine were significantly higher during the constant iv infusion of 500 :g/kg vs. 200 :g/kg in rabbits pretreated with diltiazem. This dose effect was not apparent in control rabbits. (Supported in part by a grant-in-aid from Heart & Stroke Foundation of Nova Scotia).

#### 66 3-HYDROXY-4,9-DIHYDRO-ISOTHIAZOLO[5,4-B]QUINOLINE-4-ONES AS TOPO-II INHIBITORS WITH ANTITUMOR ACTIVITY

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**Purpose:** Based on the previously reported topo-II inhibitory and anticancer activity of 8-oxo-1,2,4-thiadiazolo[4,5-*a*]quinoline-9-carboxylic acids (I) and application of structure-based molecular modeling approach, we designed and synthesized novel 3-hydroxy-4,9-dihydro-isothiazolo[5,4-*b*]quinoline-4-one derivatives (II) in order to investigate the potential of these molecules as selective inhibitors of topoisomerase-II and potential antitumors. **Methods:** Using Hyperchem program, the optimum geometry of I (R<sub>1</sub>, 5-F; R<sub>2</sub>, Ph) was determined through molecular mechanic optimization. Based on the above data, the linear analogue II (R<sub>1</sub>, 7-F; R<sub>3</sub>, CH<sub>2</sub>Ph) was designed, which was perfectly overlapping with the optimized geometry of compound I.



Compound II was then synthesized through different synthetic approaches. **Results:** Preparation of compound II was achieved by either conventional synthesis of the relevant 2-mercaptoquinolone carboxylic acid followed by N-alkylation and cyclization, or through convergent synthesis starting with appropriate benzoylacetate intermediate and further cyclization. The synthesized compounds were evaluated for their topo-II inhibitory and cytotoxic activity. Based on the success-

ful synthesis of parent N<sub>9</sub>-benzyl analogue, and in order to study the effect of different substituted alkyl, cycloalkyl, aryl, and heteroaryl moieties on the overall Topo-II inhibitory and cytotoxic activities of this class of compounds, several new N<sub>9</sub>-substituted analogues of structure **II** were synthesized and evaluated for the targeted activities. **Conclusions:** Through this study, we were able to introduce novel synthetic methodologies for the preparation of linear isothiazolo-quinolone derivatives with potential topo-II inhibitory and cytotoxic activities.

#### 67 DESIGN AND SYNTHESIS OF NOVEL SMALL HETEROCYCLES WITH POTENTIAL ACTIVITY AGAINST SYSTEMIC AND DEEP-SEATED MYCOSIS

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**Purpose:** Synthesis and evaluation of small heterocyclic molecules of isothiazol-3-one class as potential antifungal agents with improved antifungal activity and reduced cytotoxicity. **Methods:** The building blocks (unsubstituted and 5-chloro-substituted isothiazol-3-one) were synthesized and allowed to react with ammonia to yield 3,3'-dithiodiproionamide, further reaction of which with sulfonyl chloride resulted in the formation of the targeted scaffolds. Reaction of these scaffolds with appropriately substituted isocyanate derivatives gave rise to new urea derivatives. The new compounds were purified by silica gel column chromatography and their structures were determined by NMR and MS methods. The antifungal evaluation against several pathogenic fungi, including *Candida albicans*, *Candida krusei*, *Aspergillus flavus*, *Aspergillus fumigatus*, *Trichophyton mentagrophytes*, and *Trichophyton rubrum*, was performed using agar dilution method. The cytotoxicity test was performed against HeLa and CEM cell lines. Amphotericin B (AmB) was used as the reference compound in both bioassays. **Results:** Several 2-(4-substituted-phenylaminocarbonyl)-isothiazol-3-one and/or 2-(4-substituted-phenylaminocarbonyl)-5-chloroisothiazol-3-one derivatives were synthesized and tested for antifungal activity and cytotoxicity. As expected, most of the isolated compounds exhibited mild to strong antifungal activities against the fungal strains, comparable to those of AmB. In general, the antifungal activities of the 5-chloroisothiazolone derivatives were superior to those of their relevant unsubstituted analogues, indicating the importance of 5-chlorosubstituent in this series of compounds. The cytotoxicity assays demonstrated that these compounds were more cytotoxic compared to AmB, although the toxicity profiles were improved compared to the lipophilic analogues which was previously prepared by our group. **Conclusions:** The results obtained in our study indicate that through introduction of less lipophilic moieties, it is possible to decrease the cytotoxicity of this novel class of antifungal compounds while retaining their antifungal activity. Further structural modification to

improve the cytotoxicity profile of these compounds is in progress. **Acknowledgements:** Funding for this project was partly provided by Merck Company Foundation (National Summer Student Research Program).

#### 68 SEAL OIL ENHANCED TAXOL-INDUCED CYTOTOXICITY AND APOPTOSIS IN BREAST CARCINOMA MCF-7 AND MDA-MB-231 CELL LINES

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**Purpose** Some studies suggest that  $\omega$ -3 polyunsaturated fatty acids (PUFAs) are beneficial in inhibiting the growth of breast cancer cells. Considering that  $\omega$ -3 PUFAs are present abundantly in seal oil, we investigated the effect of seal oil on the cytotoxicity and apoptosis induced by taxol in certain breast cell lines. **Methods** Breast cancer cell lines, MCF-7 and MDA-MB-231, were treated with taxol alone and in combination with seal oil for 24 hrs. Cell viability was evaluated by MTT assay. Apoptosis was investigated by morphological changes and DNA strand break assay. Western blotting was used to assess the expression of p53 and Bcl-2 proteins. The intracellular lipid composition was determined by gas chromatograph and the lipid peroxide was measured by TBARS assay. **Results** IC<sub>50</sub> determined by MTT assay showed that taxol in combination with seal oil resulted in enhanced cytotoxicity in both cell lines, in comparison with taxol alone. The IC<sub>50</sub> values of taxol alone and in combination with 1.6% seal oil in MCF-7 were 15.2±4.5  $\mu$ M and 4.6±1.8  $\mu$ M, respectively. The IC<sub>50</sub> values of taxol alone and in combination with 1.6% seal oil in MDA-MB-231 were 57.0±6.6  $\mu$ M and 24.1±2.2  $\mu$ M, respectively. Apoptosis assessed using morphological changes and DNA strand break assay indicated that more cells treated with taxol in combination with seal oil were found undergoing apoptosis than that with taxol alone. Seal oil alone was also found cytotoxic and induced apoptosis in the two cell lines. Western blotting showed that the expression of apoptosis inhibitor Bcl-2 protein in both cell lines was down regulated by seal oil. Total  $\omega$ -3 PUFAs was found to have increased significantly in the lipid composition of the cells following incubation with seal oil, which may be responsible for the increased lipid peroxides found in cells incubated with seal oil. **Conclusion** Seal oil was found to enhance the cytotoxicity and apoptosis induced by taxol in both breast cancer cell lines, which may be due to its ability to down-regulate the expression of Bcl-2 protein and to produce lipid peroxides.

#### 69 ANTI-CANCER ACTIVITY, PHARMACOKINETICS, AND METABOLISM OF PICEATANNOL IN VITRO AND IN VIVO

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Piceatannol is a stilbene found in grapes, rhubarb, and sugarcane. There are no methods to quantify piceatannol in biological matrices. **Purpose:** Evaluate Piceatannol in cancer cell lines, examine activity in colorectal cancer model *in vivo*, develop a method to quantify Piceatannol in biological matrices and elucidate its metabolic pathways. **Methods:** Piceatannol (0-1000 mg/mL) was incubated with HL-60, HCT-116, MDA-MB-231, H-460, SK-N-MC, and A-375 cancer cells and viability was measured. Piceatannol 1 mg/kg was administered in the azoxymethane-induced colon cancer model and aberrant crypts counted. A novel method of measuring piceatannol and metabolites was also developed using high performance liquid chromatography. The column used was a phenomenex C18 column with fluorescence excitation 320 nm and emission 420 nm. Calibration curves were linear from 0.05 - 100 mg/mL. Extraction efficiency > 95%, bias < 7%, precision <10%, and within 10% at the limit of quantitation (0.05 ng/mL). Mobile phase was methanol and 0.04% phosphoric acid (34:66, v/v), flow rate 1.0 ml/min. Phase I and II metabolism was evaluated in male rat liver and small intestinal microsomes. Male Sprague Dawley rats (N=5; ~160 g) were cannulated and dosed intravenously and orally with piceatannol (10-40 mg/kg). Blood samples were collected over 24 h. **Results:** Piceatannol demonstrated concentration-dependent activity in the cancer cell lines tested with greatest activity in leukemia cells, IC<sub>50</sub> 5 mg/mL. Piceatannol demonstrated ~50% reduction of aberrant crypts. Piceatannol is bioavailable. Phase I metabolism revealed a minor oxidative metabolite. However, phase II metabolism revealed two glucuronidated metabolites, one major metabolite and one minor confirmed to have *m/z* of 419.3, consistent with glucuronidation. **Conclusions:** Z-Piceatannol is an active anti-cancer agent. The developed HPLC assay is sensitive and accurate. Minor phase I metabolism occurs, however phase II conjugation predominates.

#### 70 PINOSYLVIN: METHOD OF ANALYSIS, ANTI-CANCER ACTIVITY AND METABOLISM

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Pinosylvin is a stilbene found in various species of pine tree, tea oils, and herbal products. There are no validated analytical methods to quantify pinosylvin in biological matrices. **Purpose:** Evaluate the activity of pinosylvin in cancer cell lines; develop a reliable method to quantify pinosylvin in biological matrices and to determine its metabolic pathways. **Methods:** Pinosylvin (0-1000 mg/mL) was incubated with several cancer cell lines

including: HL-60, HCT-116, MDA-MB-231, SK-N-MC, and A-375 cancer cells and cell viability was measured. A novel method of measuring pinosylvin and metabolites was developed using high performance liquid chromatography with an amylose carbamate column with UV detection at 308 nm. The mobile phase used was acetonitrile and 0.1% phosphoric acid (42:58, v/v) and flow rate was 0.50 ml/min. Phase I and II metabolism was assessed *in vitro* using male rat liver and intestine microsomes. Male Sprague Dawley rats (N=5; ~160 g) were cannulated and were dosed intravenously. Blood samples were collected over 24 hours. Urine was collected over 96 hours. **Results:** Pinosylvin demonstrated concentration-dependent activity in all cancer cell lines tested, with greatest activity in MDA-MB-231 cancer cells, IC<sub>50</sub> 15 µg/mL. Phase I metabolism revealed a minor oxidative metabolite resveratrol. Phase II metabolism revealed a glucuronidated metabolite. Mass spectrometry confirmed this metabolite to have a parent *m/z* of 387.3 and a fragmentation pattern consistent with glucuronidation. Analysis of *in vivo* data revealed the presence of a glucuronidated metabolite in the serum and urine a short plasma half-life <60 minutes and <10% renal excretion suggesting biliary excretion predominates. **Conclusions:** Pinosylvin is an active anti-cancer compound. The developed HPLC assay is sensitive, reproducible and accurate. Phase I metabolism to resveratrol occurs *in vitro*. Phase II glucuronidation predominates with the glucuronidated metabolite present in urine and serum.

#### 71 STEREOSPECIFIC DISPOSITION OF THE CHIRAL FLAVANOLS HESPERETIN AND HESPERIDIN IN RODENTS, HUMANS, AND CITRUS FRUIT JUICES

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Hesperidin is a chiral flavanone glycoside found in citrus fruits and herbal products. The rutinose sugar is cleaved to leave the aglycone hesperetin. There is no stereospecific data on its disposition. **Purpose:** Develop a stereospecific method to directly quantify hesperetin and indirectly quantify hesperidin in biological matrices, and evaluate stereospecific disposition and racemic activity in colon cancer. **Methods:** A novel assay method was developed to separate hesperetin into its enantiomers using high performance liquid chromatography with a Chiral Pak AD-RH column, UV detection at 298 nm and internal standard 7-ethoxycoumarin. The mobile phase was acetonitrile / 0.01% phosphoric acid (42:58, v/v); flow rate 0.80 ml/min. Calibration curves for each enantiomer were linear 0.5-100 mg/mL. Extraction efficiency was > 99%, bias < 6.1%, precision <5%, and within 5.6% at the limit of quantitation (0.5 µg/mL). Male Sprague Dawley rats (N=10; ~200g) were cannulated and

dosed orally with hesperetin (200mg/kg), hesperidin (200 mg/kg), or orange juice (10 mL) and intravenously with hesperetin (20 mg/kg) or hesperidin (20 mg/kg). Blood samples were collected over 24 h and urine was collected over 36 hours. Healthy human volunteers (N=4) consumed 708 mL orange juice and urine collected over 36 hours. Hesperetin (0-1000 mg/mL) was incubated with HCT-116 cells and viability measured. **Results:** The presence of S-hesperidin predominates with no free hesperetin in citrus fruits. Marked stereospecificity and poor bioavailability is evident in the disposition of hesperidin and hesperetin with the predominant enantiomer in the R-configuration. Phase II glucuronidation occurred in both urine and plasma. A reduction in HCT-116 colon cancer cell viability occurred in a concentration-dependent manner with an  $IC_{50}$  of 150  $\mu\text{g/mL}$ . **Conclusions:** The HPLC assay is sensitive, accurate and stereospecific. Chiral flavonoids are an overlooked class of active natural products that demonstrate stereospecificity in their disposition and perhaps action(s).

## 72 ALPHA-TOCOPHEROL SUCCINATE: ANALYSIS, CONTENT UNIFORMITY, PHARMACOKINETICS, TISSUE DISTRIBUTION AND ANTI-CANCER ACTIVITY

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(+) -a-tocopherol acid succinate (a-TS) analysis in biological fluids and commercial products is necessary for determination of *in vitro* and *in vivo* metabolism, and content uniformity. **Purpose:** Develop a direct method of quantifying a-TS and the  $\bar{A}$ ,  $\bar{A}$  isoforms as well as other tocopherol derivatives. Examine a-TS pharmacokinetics in rats, evaluate content uniformity in products and anti-cancer activity. **Methods:** High-performance liquid chromatography was used. Rat serum acidified, extracted with hexane, and precipitated with acetonitrile. A C18 column with UV detection at 205 nm and tocopherol acetate as internal standard, mobile phase acetonitrile/ $\text{H}_2\text{O}$  (95:5, v/v), flow rate 1.3 ml/min and linearity 0.005-100 mg/ml. Extraction efficiency > 92%, bias < 5%, precision < 5% and limit of quantitation (0.005 mg/ml). Canulated male Sprague Dawley rats (N=5; ~200 g) dosed intravenously with a-TS (100 mg/kg). Content uniformity of TS was determined in commercial products. Activity determined in HL-60, HCT-116, MDA-MB-231, SK-N-MC, H-69, H-460 and A-375 cells. **Results:** Serum AUC,  $t_{1/2}$ , Cl and  $V_d$  of a-TS were  $2553.3 \pm 166.4$  mg h/mL,  $9.83 \pm 0.86$  h,  $0.039 \pm 0.0027$  L/h/kg and  $0.56 \pm 0.09$  L/kg (mean  $\pm$  S.D), respectively. Distribution into tissues and a low Cl was apparent with

the highest concentrations of a-TS in liver and lung. Baseline endogenous concentrations of a-tocopherol (T) were present in both groups, however, and a net increase in T occurred as a-TS was metabolized to T which slowly peaked in serum between 7-8 h. These results indicate that a-TS preferentially delivers T and a-TS to the lung and liver tissues. Two out of 14 commercially available products contained no a-TS. a-TS demonstrated activity in each cancer cell line examined. **Conclusions:** a-TS has an anti-cancer activity and can be reliably and directly detected. a-TS content uniformity needs to be established when undertaking clinical studies.

## 73 EFFECTS OF PEGYLATION ON THE STABILITY OF YEAST CYTOSINE DEAMINASE

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**Purpose:** Yeast cytosine deaminase (yCD) catalyzes deamination of prodrug 5-fluorocytosine into cytotoxic 5-fluorouracil (5-FU) with  $k_{\text{cat}}/K_m = 5.6 \times 10^5 \text{ s}^{-1} \times \text{M}^{-1}$ . To reduce normal tissue toxicities associated with 5-FU dosing, we are interested in improving the pharmacokinetic and tumor-specific delivery of PEGylated yCD by taking advantage of the EPR effect. **Methods.** We have cloned the FCY1 gene and induced protein expression in *E. Coli* cells. The protein was isolated from crude lysate via His-tag purification in a Ni-NTA column driven by FPLC. Covalent attachment of mPEG<sub>5K</sub> chains onto the surface lysines of yCD was conducted under mild aqueous conditions (0.5M NaCl/0.5M  $\text{NH}_4\text{OAc}$ , pH 7.5). FPLC, denaturing gels and MALDI-ToF were used to characterize yCD and conjugates. **Results.** Enzyme activity studies reveal that the His-tag has no apparent effect on substrate affinity. Studies at 37°C reveal that prior to conjugate pre-incubation, order of relative activities were 4mPEG<sub>5K</sub>-yCD > yCD/BSA > 2mPEG<sub>5K</sub>-yCD > yCD > 3mPEG<sub>5K</sub>-yCD. After conjugate pre-incubation, we observed  $t_{1/2} = 8$  hrs for yCD and 2mPEG<sub>5K</sub>-yCD, whereas for 3, 4mPEG<sub>5K</sub>-yCD and yCD/BSA,  $t_{1/2} < 2$  hrs. Dissociation of homodimeric yCD and conjugates were monitored up to 30 min of incubation with FPLC. Aggregates were collected and analyzed with denaturing gels. In the case of 3 and 4mPEG<sub>5K</sub>-yCD, steric hindrance is a factor contributing against recombination and accounts for the shorter  $t_{1/2}$ . **Conclusion.** It is apparent that covalently attaching mPEG<sub>5K</sub> chains onto the surface of the enzyme provides some thermal protection but no structural stability. These studies provide the basis for the current efforts to improve the structural stability of yCD-conjugates. It is expected that more functional PEGylated yCD-conjugates can be delivered to tumor sites, leading to greater therapeutic concentrations of 5-FU at the tumor mass.

## 74 AGGREGATION AND CONFORMATION OF A THERAPEUTIC PEPTIDE CHARACTERIZED BY

**BIOPHYSICAL METHODS**

Brandon Doyle, Mark Pollo, Allen Pekar, Michael Roy,  
Beth Ann Thomas-Klotz & Mark Brader

**Purpose:** To investigate the propensity of a therapeutic peptide to form pharmaceutically undesirable aggregates in solution. A concomitant aim was to use this system to compare several biophysical methods for detecting and characterizing a small fraction of soluble, non-covalent aggregate. **Methods.** Reversible self-association of the peptide in solution was characterized by analytical ultracentrifugation at pH 3, 7.5, 9.1 and 10.5. Additional biophysical signatures of the peptide recorded under aggregating versus non-aggregating conditions were obtained using dynamic light scattering (DLS), circular dichroism spectroscopy (CD), Fourier transform infrared spectroscopy (FT-IR), dye-binding affinity, and filtration resistance. **Results.** Equilibrium sedimentation analysis showed that the peptide exists as a monomer at pH 3 over the concentration range 0.1-5 mg/mL and undergoes concentration-dependent self-association at higher pH values. Peptide lyophilized from 25% acetonitrile/50 mM acetic acid was susceptible to formation of soluble and insoluble aggregates. The presence of the soluble aggregate did not contribute measurably to secondary structure in solution as detected by CD but was evident from DLS measurements giving three nm diameters for unaggregated peptide versus species in the 60-400 nm diameter range for aggregated peptide. Soluble aggregates were identifiable by FT-IR and affinity for naphthol blue-black utilizing a dye-binding methodology. In the solid state, the effect of aggregation was evident in the FT-IR powder spectrum characterized by a distinctive band at 1625  $\text{cm}^{-1}$ . **Conclusions.** Soluble and insoluble  $\beta$ -sheet peptide aggregates were characterized as the product of a solvent-dependent physical instability. Second derivative FT-IR was found to be effective in detecting the presence of a small fraction of aggregate in solution whereas far-UV CD spectroscopy was not. This poster presented in part at 2003 AAPS annual meeting.

**75 HPLC DETERMINATION OF SELECTED FAVONOIDS IN GINKGO BILOBA SOLID ORAL DOSAGE FORMS**

M-J Dubber, *Izzy Kanfer*; Faculty of Pharmacy, Rhodes University, Grahamstown, East Cape, South Africa

**Purpose** *Ginkgo biloba*, commonly marketed as leaf extracts in pharmaceutical dosage forms, is currently one of the top selling herbal preparations with estimated world wide sales in 1998 reaching a staggering \$1 billion. The chemical components implicated for *Ginkgo biloba*'s pharmacological activity, the flavonoids and terpene lactones, are useful markers to assess the quality of *Ginkgo* preparations available to consumers. The aim of this study was to develop a method which can be used for the quality control of *Ginkgo Biloba* by quantitating 5

flavonol marker compounds in *Ginkgo biloba* dosage forms using HPLC. **Methods** The 5 relevant flavonols were separated at 45°C on a minibore Phenomenex Luna 5m  $\text{C}_{18}$  (2) column with dimensions 250 x 2.00mm using a one step linear gradient at a flow rate of 400ml/min. Mobile phase A (acetonitrile) and B (0.3% formic acid) ratios were changed after 15 minutes from 15:85 to 25:75. **Results** The selected flavonols, rutin, quercitrin, quercetin, kaempferol and isorhamnetin were successfully resolved within 33 minutes with retention times of 8.72, 14.08, 19.77, 28.06 and 31.45 minutes, respectively. This method was validated according to USP guidelines and applied to assay five commercially available solid oral *Ginkgo biloba* dosage forms based on their content of the relevant flavonol markers. **Conclusion** A simple, precise, rapid and reproducible RP-HPLC method was developed to quantitate five relevant flavonol marker compounds with successful application to several commercially available *Ginkgo biloba* dosage forms. Sample preparation was simple and no tedious cleanup was necessary. Product analysis showed similar qualitative profiles but remarkably different quantitative composition. These results indicate that suitable quality control measures need to be implemented to ensure consistent quality, safety and efficacy of *Ginkgo biloba* products.

**76 PK/PD MODELING OF AMINOGLYCOSIDES IN SEVERE BURN PATIENTS USING AN ARTIFICIAL NEURAL NETWORK**

*Shigeo Yamamura, Keiko Kawada, Rieko Takehira, Kenji Nishizawa, Shirou Katayama, Masaaki Hirano, Yasunori Momose*; Toho University, Funabashim, Chiba; Nippon Medical School Hospital, Japan

**Purpose:** To use an artificial neural network (ANN) to develop a PK/PD model for aminoglycosides in burn patients using the patients' physiological data as well as their burn severity. **Method:** Physiological data and some indicators of burn severity were collected from 30 burn patients who received arbekacin (ABK: aminoglycoside widely used for MRSA infection in Japan). A stepwise-regression analysis was performed to identify plasma concentration covariates (PK parameters) and effectiveness measures (PD parameters). An additional parameter indicating burn severity was also added to the input variables. A three-layer ANN was used and the weights among neurons were optimized using a conjugate gradient descent method. Goodness of fit for the model was evaluated using the sum of squares and Akaike's information criteria (AIC). **Results:** The best PK parameters included dose, BMI, creatinine concentration and amount of parenteral fluid. The best PD parameters included peak concentration, creatinine concentration, duration of ABK administration and blood sugar. These PK and PD parameters were used as covariate variables for the ANN. For the PK/PD modeling, the best indicator for burn severity was the burn area less the skin graft area. The optimized

ANN structure for predicting PK/PD outcomes was an ANN with five (PK model) and six neurons (PD model) in the hidden layer. Predictive performance when the ANN included burn severity was superior to a linear regression model. **Conclusion:** An ANN was a powerful tool for developing a PK/PD model based on physiological data from severe burn patients. Accounting for burn severity, as part of the PK/PD model, greatly improved the model's overall predictive performance for severe burn patients.

#### 77 DESIGN AND EVALUATION OF CARBOPOL-METHYL CELLULOSE MUCOADHESIVE FILMS FOR BUCCAL DELIVERY

*Kusum Devi and Avinash R. Mane; Department of Pharmaceutics, Al-Ameen College of Pharmacy, Bangalore, Karnataka State, India*

**Purpose:** To improve bioavailability of drugs, which undergo first pass metabolism, to achieve excellent absorption and controlled release of the drug with reduced dose and side effects through buccal drug delivery systems such as buccal patches, buccal tablets etc. **Methods:** Buccal films of carbopol-934P and methyl cellulose in combination and concentration were prepared by a casting solvent/evaporation technique with polyethylene glycol-400 as plasticizer. **Results:** In preliminary permeation studies of model drug Metoprolol Tartrate, this antihypertensive agent was studied through cellophane membrane and pig oral mucosa. Flux obtained was 0.00899 mg/cm<sup>2</sup>/min. In addition, a preliminary study indicated that drug/excipients used did not exhibit mucosal irritation. All the formulations exhibited similar thickness, with minimum weight variation (< 5.0%). Drug content was uniform from film to film and within the film ranging from 97.03±1.59 to 99.13±2.51. All prepared films showed folding endurance of more than 500 and surface pH of 6.4 to 6.7, which was similar to salivary pH. With respect to water uptake, the films with higher amount of Carbopol absorbed large quantity of water, gelled and eroded slowly. In addition, water uptake was reduced in presence of sodium ions. Furthermore, films displayed optimum tensile strength and adequate adhesive capacity. Films showed permeation of water vapor at higher rate during first 48 hours of the study, which was conducted for 7 days at 25°C and 75%RH. In-vitro drug release from films through cellophane membrane and pig oral mucosa showed sustained drug release up to 11 h with the flux ranging from 0.3017 to 0.6451 mg/cm<sup>2</sup>/min. **Conclusion:** Thus for water soluble drug like Metoprolol Tartrate the formulated films show potential for systemic controlled drug delivery of drugs through oral mucosa. As the drug directly enters the blood, first pass metabolism is overcome leading to concomitant reduction in dose and side effects.

#### 78 DUAL POLYMER CONTROLLED MINI MODIFIED RELEASE TABLETS OF GLICLAZIDE *Kusum Devi and Vijayalakshmi Prakya; Department of Pharmaceutics, Al-Ameen College of Pharmacy, Bangalore, Karnataka State, India*

**Purpose:** The objective was to develop mini Gliclazide-MR tablets with very low total weight with a newer combination of pH dependent polymers like Keltone-HVCR and Eudragit-EPO powder for use particularly in geriatrics. **Methods:** Keltone-HVCR, a sodium-alginate derivative, is soluble above pH-4 whereas Eudragit-EPO powder is soluble below pH-5, the former controls drug release in gastric region and latter, which is swellable and permeable above pH-5, controls drug-release in intestine thus releasing drug through out GIT for extended period. Various tablet batches containing different ratios of polymers and additives like lactose and pladone-K90D were prepared. Total tablet weight ranging from 65mg to 75mg was punched using 6mm punches to 4kg/cm<sup>2</sup> hardness. All batches of formulated tablets had acceptable physicochemical properties. Dissolution studies were carried out in various pH buffers viz., pH-1.2 (for 2 hours), pH-4.5 (for 2 hours) and pH-6.8 (until all drug released). Every 1 hour, amount of drug released was analysed as per BP-2001. Drug-release-profile was also compared with marketed brand of Gliclazide, Diamicon MR-30mg tablets. **Results:** All formulations including marketed, released 100% of drug within 7 hours. Drug-release-profile from tablets with lowest total weight of 65mg, containing 10mg of each polymer in 1:1 ratio, extended drug release in a well-controlled manner in varying pHs ( $r^2=0.9819$ ). Whereas, other batches along with marketed tablets, had sharp peaks and valleys in drug-release-profile. Drug release rate almost doubled for all formulated tablets at pH-4.5 buffer, which may be due to both the polymers being soluble at a pH of 4-5. **Conclusion:** Drug-release-profile from most satisfactory formulation was well controlled and uniform throughout the GIT and total weight of formulated tablets was less than half of marketed tablets. Mechanism of drug release from formulated tablets was diffusion, which was concluded from Higuchi's plot.

#### 79 AMPICILLIN BIOSYNTHESIS USING CROSS-LINKED AGGREGATES OF PENICILLIN G ACYLASE

*Abedi Dayoush, Fazeli M.R., Jafarian Dehkordi A.*

**Purpose:** The enzymatic synthesis of  $\beta$ -lactam antibiotics such as ampicillin offers several benefits compared to conventional chemical methods. The enzymatic procedure is carried out under mild conditions in water, with no need for protection/deprotection schemes and is environmentally benign. Penicillin acylases (EC 3.5.1.11) are a group of enzymes that cleave the acyl chain of penicillins to yield 6-Amino penicillanic acid (6-APA) and can be used in the reverse synthesis of  $\beta$ -lactam

antibiotics from the corresponding  $\beta$ -Lactam nuclei and suitable acyl donor. We tried to immobilize penicillin acylase from *E. coli* TAI for production of ampicillin using a Cross-Linked Enzyme Aggregation (CLEA) method described by Sheldon *et al.* which involves the physical aggregation of the enzyme under non-denaturing conditions followed by cross-linking to cross-link enzyme aggregates. Cross-Linked Enzyme Aggregates (CLEA) and commercial immobilized penicillin G acylase (PGA-450) were used to study the effect of pH and temperature and substrate concentration on the synthesis of ampicillin from phenyl glycine methyl ester (PGME) and 6-aminopenicillanic acid (6-APA). **Methods:** CLEAs were prepared by slowly adding *tert*-butanol to penicillin G acylase solution under gentle stirring at 0 °C. When no more activity was detected in the supernatant, the physically aggregated penicillin G acylase was subjected to chemical cross-linking using glutaraldehyde (25% aqueous solution) at 0°C. The CLEAs were then collected by filtration and washed with phosphate buffer (50 mM, pH 7) and dispersed in buffer and stored at 4 °C before use. The synthesis activity of biocatalysts was determined in a batch reactor at 25 °C. The ampicillin concentration was determined by High Performance Liquid Chromatography (HPLC). **Results:** Effect of substrate concentration on production of Ampicillin by free enzyme and CLEA (5 U/ml) at pH 6, t 25°C. **Conclusion:** We managed to successfully immobilize penicillin G acylase based on CLEA method and show that the product acts even better than the commercial one. Although the results obtained in this study are far from industrially acceptable biocatalyst however could be used for development of a CLEA based penicillin G acylase in industrial production. Comparison of the different forms of the enzyme and optimization of the activities, especially ampicillin production are the other important outcomes of this research, which can be used in further researches in this field.

#### 80 5 $\alpha$ -REDUCTASE INHIBITORY ACTIVITY OF NEW ACYLOYLOXY PREGNA-4, 16-DIENE-6,20-DIONE DERIVATIVES

Marisa Cabeza, Eugene Bratoeff, Mauricio Sánchez, Ivonne Heuze, Norma Valencia, Elena Ramírez; Metropolitan University of México, Calzada del Hueso; and National University of Mexico, Ciudad Universitaria, Mexico, D.F. Mexico

The enzyme 5 $\alpha$ -reductase is responsible for the conversion of testosterone (T) to its more potent androgen dihydrotestosterone (DHT). This steroid had been implicated in androgen dependent diseases such as benign prostatic hyperplasia, prostate cancer, acne and androgenic alopecia. The inhibition of 5 $\alpha$ -reductase affords a potentially useful treatment for these diseases. **Purpose:** In this study, we report the synthesis and pharmacological evaluation of several new 3-substituted pregna-4, 16-diene- 6, 20-dione derivatives. These

compounds were prepared from the commercially available 16-dehydropregnenolone acetate. The biological activity of the new steroidal derivatives was determined *in vivo* as well as *in vitro* experiments. **Methods:** *In vivo* experiments, the antiandrogenic effect of the steroids was demonstrated by the decrease of the diameter of the pigmented spot of the flank organs as well as the decrease of the weight of the prostate gland of gonadectomized hamster treated with T plus finasteride or the new steroids. The IC<sub>50</sub> value of these steroids was determined by measuring the conversion of radiolabeled T to DHT. **Results:** The results of this study indicated that the four steroidal derivatives showed a much higher 5 $\alpha$ -reductase inhibitory activity, as indicated by the IC<sub>50</sub> values than the presently used Proscar (finasteride). In the flank organ model, compounds N<sub>3</sub> and N<sub>4</sub> exhibited a significantly lower diameter of the spot thus indicating a higher *in vivo* inhibitory activity. **Conclusion:** The comparison of the weight of the hamster prostate gland indicated that compound N<sub>2</sub> had a comparable weight decrease as finasteride. The overall data of this study showed very clearly that all four steroids derivatives are good inhibitors for the 5 $\alpha$ -reductase enzyme.

#### 81 MOLECULAR AND TISSUE MECHANISMS OF HYALURONIC ACID IN THE WOUND HEALING Loida Ourña, Guillermo Lago, Gabriel Coto; Center State of Quality Control of Drug; Placental Hystoterapeutic Center

By the therapeutically important of the Hyaluronic Acid (HA) as healing, we profound the use of it and the action mechanism in skin. **Purpose** We showed that molecular and tissue mechanism of HA extracted from umbilical cord residual in accelerating wound healing. **Methods** The molecular and cellular level mechanism's action using HA in rats skin was studied. The histopathology slide of sample of epidermis from rat's skin was processed too. **Results** We showed that specimen treated with HA have a lineal in three times more than the control group. It was developed by planimetric methods; the best epithelial migration evolution was shown morphometric, and histopathologically The reepitelization was 21.8% more elevated than the control. It is based in the growth, proliferation and cellular differentiation due to basal cells from epidermis with specific receptors as to CD 44. HA to increase the specific change of the keratinocytes promoting the elongation and migration of wound margins together to the myofibroblast allow the wound contraction On the other hands the accelerate dermal reconstitution in the 20 time more the testing group was due for its interaction between CD44 receptors in epithelial cells with extracellular matrix (ECM) into and the integrin-fibronectin system, moreover possibility the synthesis of ECM for the fibroblast thus its contract an remodeling was induce for the presence of HA, contribute in the reorganisation of the fibber collagen add, together to influence in the reconstruc-



tion of the ECM for the posterior presence in the scar of the wound. **Conclusion:** the interaction of the HA with the CD44 receptors and the complex integrin-fibronectin is the responsible its action mechanisms. This is considerate a promoter of grow tissue and a production inductor and reconstruction of ECM inductor.

## 82 ISOLATION OF HYALURONIC ACID FROM UMBILICAL CORD RESIDUAL USED AS WOUND HEALING IN RATS

*Guillermo Lago, Loida Oruña, José A. Cremata, Gabriel Coto; Centro de Histoterapia Placentaria; Centro Estatal para el Control de Medicamentos; Centro de Ingeniería Genética y Biotecnología*

Hyaluronic acid (HA) is a polysaccharide present in the connective tissue of all body and has very therapeutically effect. **Purpose.** In the present paper, we show a novel method for the isolation, purification, characterization and use of it from human umbilical cord residual. **Methods.** The polysaccharide was extracted with sodium chloride solution and sediment by adding of cetyltrimetilamonium bromide (CTAB) at 1% and calcium chloride at 0.9 mol/L was used in order to break the AH-CTAB complex. The HA was sediment by adding ethanol later. The product was purified by adding of chloroform in three stages and it was characterized by chemical methods as protein, uronic acid, reductive sugars tests and physico-chemicals methods as the liquid chromatographic employing the reverse phase (RP) and the ion exchange chromatographic and then the spectroscopic methods were used as the infrared spectroscopic and carbon  $^{13}\text{C}$  NMR ( $^{13}\text{C}$  Nuclear Magnetic Resonance ) by decoupling methods and we compare the experimental sample with a reference standards. The HA at 4% in jelly was evaluated as healing in rats. **Result** The HA yield was around 40 gr/ kg of human umbilical cord residual which is elevate. The statistic test was used for the evaluation of 15 samples again. We found that the variation's coefficient for the percentage HA was < 10 and in the others analytical methods < 5 and the level of protein was below in comparison with others biological sources. The retention time of the HA in both chromatographic methods were similar to the reference standards and the principal bands in IR spectrum and the chemicals shifts in  $^{13}\text{C}$  NMR may be compared with the patron. The product show healing activity in jelly form to the 4% tested in rats. **Conclusions** We development a new methods for the isolation of HA from the human umbilical cord residual no reported as biological source in the literature. The product may be used as wound healing in rats

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**Notes**

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Website: www.ualberta.ca/~csp

### *Society Mission*

The mission of the Canadian Society of Pharmaceutical Sciences is to establish a network of pharmaceutical scientists in Canada, and make contact with sister national/international agencies in pursuit of excellence in research, development and training. The specific goals of the CSPS are:

- To advocate excellence in pharmaceutical research
- To promote allocation of funds for pharmaceutical research
- To be involved in decision and policy making processes at the government level
- To encourage the continued development of an improved environment for industry-based pharmaceutical research

### *Executive Council*

- McKay, Gordon: President, 2004-2005
- Vadas, Elizabeth: Past-President, 2004-2005
- Masson, Eric: Past-President, 2003
- Yeung, Pollen: Treasurer, 2003-2004
- Endrenyi, Laszlo: Secretary, 2003-2004
- Jamali, Fakhreddin: Appointed By The Executive
- Piquette-Miller, Micheline: Member-At-Large, 2004-2008
- Sayani, Aryn: Member-At-Large, 2003-2007
- Brocks, Dion: Member-At-Large, 2003-2006
- Dolphin, David: Member-At-Large, 2004-2005
- Kotra, Lakshmi: Member-At-Large, 2004-2004

### *Contact Information*

CANADIAN SOCIETY FOR PHARMACEUTICAL SCIENCES  
SOCIÉTÉ CANADIENNE DES SCIENCES PHARMACEUTIQUES  
7<sup>TH</sup> SYMPOSIUM  
9-12 JUNE 2004  
VANCOUVER, BRITISH COLUMBIA  
Canada

**Molecule to market: biotechnologically-derived molecules vs traditional small chemical entities.**

**Symposium Sessions**

- New challenges to drug discovery: small synthetic and biotech-derived chemical entities.
- Analytical issues related to synthetic and biotech-derived molecules.
- Special considerations in formulating new chemical entities derived from biotechnology.
- Special topics in pharmacokinetics and drug metabolism: small synthetic and biotech-derived entities.
- Regulatory issues faced in development of small synthetic and biotech-derived entities.
- Round table discussion: pharmaceutical scientists and society: is the supply meeting the demand?
- Poster presentations.

*Conference proceedings will be published in the Journal of Pharmacy & Pharmaceutical Sciences.*