PHARMACY RESEARCH DAY

APRIL 25, 2018

10 years

BOLD START
BRIGHT FUTURE

UNIVERSITY OF WATERLOO
FACULTY OF SCIENCE
School of Pharmacy

CONTENTS

FOREWORD

SHAWN WETTIG, PhD, CChem
ASSOCIATE DIRECTOR, GRADUATE STUDIES AND RESEARCH
SCHOOL OF PHARMACY, UNIVERSITY OF WATERLOO

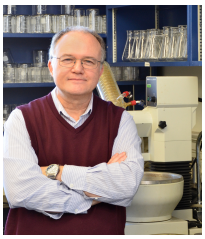
On the occasion of our 10th anniversary, I am particularly pleased to welcome you to the second annual Pharmacy Research Day. Research day provides an opportunity for us to showcase the leading edge research of graduate students and post-doctoral fellows conducting research in fields related to Pharmacy. Our students are engaged in research ranging from the understanding of complex cellular mechanisms involved in cancer to novel methods for the delivery of drugs, and ultimately to the various factors that influence a pharmacist's decision making in the management of medications. The research activities of our students truly bridge the bench-to-bedside gap in healthcare related research.

As Canada's youngest School of Pharmacy, we have seen extraordinary growth in our collective research activities over our first decade of operations. We have grown from a faculty of just five research scientists in 2007, to a total of 21 full-time research faculty and 35 adjunct faculty members; many of whom are also involved in research within the School. Our MSc and PhD programs were approved in 2011 and 2013, respectively, with our current enrollment being 16 MSc and 23 PhD students. Since 2009, our faculty members have raised over $15 million to support research within the School of Pharmacy.

I am excited about our future as we continue to grow our research program at the School of Pharmacy, and even more so to have the opportunity to showcase our amazing graduate students and faculty; not only to the larger University of Waterloo family, but also within the Province of Ontario, nationally, and internationally. In keeping with the School of Pharmacy's vision, our research efforts are leading transformative change in the development and use of medications for the improvement of human health.

Thank you for attending Pharmacy Research Day 2018!

KEYNOTE SPEAKER



DONALD F. WEAVER, MD, PhD, FRCPC
DIRECTOR AND SENIOR SCIENTIST, CANADA RESEARCH CHAIR, TIER 1, KREMBIL RESEARCH INSTITUTE
NEUROLOGIST, UNIVERSITY HEALTH NETWORK
PROFESSOR OF NEUROLOGY, CHEMISTRY AND PHARMACEUTICAL SCIENCES, UNIVERSITY OF TORONTO

Donald Weaver is Director and Senior Scientist of the Krembil Research Institute, University Health Network; he is also a professor of neurology, pharmacy and chemistry at the University of Toronto. Dr. Weaver initially trained as a physician obtaining his MD from Queen's University, later qualifying as a neurologist. Subsequently he completed a PhD in medicinal chemistry. He has held faculty positions at Queen's University, Dalhousie University and the University of Toronto. He has also co-founded eight start-up biotech companies and has had two compounds reach Phase III human clinical trials.

Design and development of disease modifying drugs for Alzheimer's dementia

A looming threat, and one for which we are woefully underprepared, is Alzheimer's disease (AD). AD is an age-related and ultimately fatal, degenerative dementia. As lifespans increase around the world, and the baby-boomer generation approaches old-age, AD is becoming increasingly common. At present, there are 7.7 million new cases per year worldwide – that's a new case of AD every four seconds. The number of people with Alzheimer's is projected to rise and by 2050 more than 135.5 million people will be struggling with (and ultimately dying from) AD. Of the last 196 clinical trials of putative "curative" agents for AD, all have failed. Currently, multiple hypotheses exist for the cause of AD, with the two leading ones being proteopathy (misfolding of beta-amyloid and/or tau protein) and immunopathy (release of pro-inflammatory cytokines from microglial cells). Our approaches in computer aided drug design targeting both of these hypotheses through druggable targets will be presented.

PROGRAM

9:00 – 9:05 a.m. **DIRECTOR'S WELCOME**

PHR 1004 David Edwards, Hallman Director, School of Pharmacy
Associate Dean, Faculty of Science, University of Waterloo

9:05 – 9:55 a.m. **KEYNOTE PRESENTATION**

PHR 1004 Donald F. Weaver, Director and Senior Scientist, Canada Research Chair, Tier 1, Krembil Research Institute; Neurologist, University Health Network; Professor of Neurology, Chemistry and Pharmaceutical Science, University of Toronto
Design and development of disease modifying drugs for Alzheimer's dementia

10:00 – 12:00 p.m. **CONCURRENT ORAL PRESENTATIONS**

10:00 – 10:25 a.m. **SESSION 1**

PHR 1008 Pierre Chelle, PhD, Postdoctoral Fellow, School of Pharmacy
Comparison of population PK and non-compartmental analyses for tailoring PK in hemophilia A with limited samples

PHR 1012 Monica Hoang, PhD Candidate, School of Pharmacy
Effects of diet-induced diabetes on β-cell specific aryl hydrocarbon receptor nuclear translocator/ hypoxia-inducible factor-1β (ARNT/HIF-1β) knockout mice

10:30 – 10:55 a.m. **SESSION 2**

PHR 1008 Gokul Raj Pullagura, PhD Candidate, School of Pharmacy
Economic analysis of introducing community-pharmacist led influenza vaccine consultation service for Ontario seniors

PHR 1012 Alanna McEneny-King, PhD Candidate, School of Pharmacy
The WAPPS-Hemo project: an innovative approach to individualized prophylaxis

11:00 – 11:25 a.m. **SESSION 3**

PHR 1008 Amna El Shatshat, MSc Candidate, School of Pharmacy
Interactions of polyunsaturated fatty acids with amyloid beta (Aβ) proteins

PHR 1012 Ben Kim, PhD Candidate, School of Public Health and Health Systems
A review of the accuracy and comprehensiveness of the pharmaceutical information within drug to drug interaction mobile applications

11:30 – 11:55 a.m. **SESSION 4**

PHR 1008 Paul Malik, PhD Candidate, School of Pharmacy
A physiologically-based approach to the pharmacokinetics of anti-TNF agents in pediatrics

PHR 1012 Morgan Robinson, PhD Candidate, School of Pharmacy
Amyloid-β inhibitor drugs for Alzheimer's disease: from rational design to cell viability

12:00 – 12:25 p.m. **SESSION 5**

PHR 1008 Yannick Traore, PhD Candidate, School of Pharmacy
Nanoparticles-coated intravaginal ring for dual delivery of siRNA and hydroxychloroquine against HIV infection

PHR 1012 Kathryn Mercer, PhD Candidate, School of Pharmacy
Building bridges: how research changes in multi-disciplinary patient inclusive settings

12:30 – 1:30 p.m. **LUNCH**

1:00 p.m. **MESSAGE FROM THE DEAN**

Bob Lemieux, Dean of Science
Professor, Department of Chemistry, University of Waterloo

1:00 – 3:00 p.m. **POSTER PRESENTATIONS**

2nd Floor Foyer

3:00 p.m. **CLOSING REMARKS**

Bernard Dunker, Associate Dean of Science for Research
Professor, Department of Biology, University of Waterloo

RESEARCH ABSTRACTS

ORAL PRESENTATIONS

Comparison of population PK and non-compartmental analyses for tailoring PK in hemophilia A with limited samples

PIERRE CHELLE[1,*], ALANNA MCENENY-KING[1], YEJIN YUN[1], ALPHONSO IORIO[2], ANDREA N EDGINTON[1]

Introduction: Hemophilia A is a bleeding disorder characterized by the deficiency of coagulation factor VIII. Standard treatment to prevent bleeds aims at infusing the patient with the missing factor to target a trough FVIII level above 1%. Individual pharmacokinetic (PK) estimation is essential to tailor treatment and usually performed by blood sampling and non-compartmental analysis (NCA). NCA requires many blood samples whereas population pharmacokinetic (popPK) modelling requires fewer samples and might be better suited to this task. The objective was to assess if a popPK model provides equivalent PK estimates to NCA with limited samples. **Methods**: A virtual dataset was created with 1000 subjects having observations at predose, 1,3,6,12,24,48 and 72h post infusion (rich data) based on a popPK model [1]. PK parameters were estimated and compared between NCA and Bayesian forecasting from the popPK model. Data subsets having only 3 observations (sparse data) were also compared. **Results**: Comparison between the methods using on rich data led to a 7% median error and R2 of 0.68 for half-life. Using sparse data at predose, 48 and 72h or predose, 1 and 48h led to a median error lower than 10% and R2 higher than 0.62. Similar results were obtained with other PK parameters. **Conclusion**: The correlation between PopPK model and NCA outcomes using rich or sparse data was similar. Therefore, PopPK models are well suited for individual PK estimation with few observations and limited sampling analysis is a useful diagnostic tool that assesses the efficiency of limited sampling strategies.

[1] Zhang Y, Roberts J, Tortorici M, Veldman A, St Ledger K, Feussner A, Sidhu J. Population pharmacokinetics of recombinant coagulation factor VIII-SingleChain in patients with severe hemophilia A. J Thromb Haemost 2017; 15: 1106–14

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Interactions of polyunsaturated fatty acids with amyloid beta (Aβ) proteins

AMNA EL SHATSHAT[1,*], PRAVEEN NEKKAR RAO[1]

Purpose: In the past couple decades, our understanding of diet and which type of foods are considered to have the highest nutritional benefit has varied greatly. The link between our dietary intake and what these compounds actually do to our bodies has increased our collective anxiety around diet. The food we consume has an effect on the progression of a multitude of various disorders. Environmental factors play a key role in the progression of neurodegenerative diseases, such as Alzheimer's disease (AD). In this regard, polyunsaturated fatty acids (PFAs) are known to be involved in AD pathophysiology. AD is characterized by the formation of dense neurotoxic amyloid β plaques. The mode of action by which these PFAs increase or decrease cognition in AD patients has only been hypothesized, and the direct interaction between PFAs and Aβ40 and Aβ42 peptides is not clearly understood. **Objective**: The objective of this study was to study the interactions of various PFAs on Aβ40 and Aβ42 peptide aggregation in order to gain insight on the effects of dietary PFAs on AD pathophysiology. **Method**: This project employed biochemical assays, imaging and computational chemistry in order to study the interaction of Aβ40/42 peptides. **Conclusion**: The results obtained indicate the anti-aggregation activity exhibited by PFAs toward Aβ40/42 suggesting their application in the design of new anti-AD therapies.

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Effects of diet-induced diabetes on β-cell specific aryl hydrocarbon receptor nuclear translocator/hypoxia-inducible factor-1β (ARNT/HIF-1β) knockout mice

MONICA HOANG[1,*], JAMIE JOSEPH[1]

Purpose: The transcription factor ARNT/HIF1β plays a key role in maintaining pancreatic β-cell function. β-cell ARNT/HIF1β regulates glycolysis, anaplerosis, NADPH/NADP+ ratio, Ca2+ influx and has also been shown to be one of the most down regulated transcription factors in islets from type 2 diabetic patients. Using a β-cell specific ARNT/HIF1β knockout (β-ARNT KO) mouse model, we have shown a strong role for ARNT/HIF1β in glucose sensing and insulin secretion in vitro. However, β-ARNT KO mice have no significant in vivo defects associated with glucose tolerance and insulin resistance. **Method**: In order to gain a better understanding of the role of ARNT/HIF1β in the development of diabetes, we placed male β-ARNT KO mice on either a chow diet consisting of 5.5% fat or a HFD consisting of 58% fat with sucrose for 10 weeks. **Results**: The only in vivo significant difference seen for β-ARNT KO mice on the HFD was that they had no impairment in glucose tolerance and had a significantly elevated plasma insulin during the ipGTT compared to HFD fed control mice. β-ARNT KO mice had lower β-cell mass on a chow diet as compared to chow fed control mice and showed no further impairment on the HFD. Isolated β-ARNT KO islets from chow fed mice and islets from HFD fed control mice had impaired GSIS and glucose-stimulated NADPH/NADP+ ratio responses as compared to control diet fed mouse islets. Isolated islets from β-ARNT KO mice on the HFD showed an improvement in GSIS and NADPH/NADP+ ratio response to glucose suggesting that the defects seen in the control fed β-ARNT KO islets could be rescued by a HFD. **Conclusion**: We have shown a consistent role for ARNT/HIF1β in the maintenance of β-cell function in vitro and β-cell mass.

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A review of the accuracy and comprehensiveness of the pharmaceutical information within drug to drug interaction mobile applications

BEN KIM[1], ANIS SHARAFODDINI[1], NAM TRAN[1], **EMILY WEN**[1], JOON LEE[1]

Objective: To provide quantitative information about the accuracy and comprehensiveness of the pharmaceutical data presented to consumers by drug to drug interactions (DDIs) mobile applications (apps). **Design and Methods:** A total of 23 relevant apps were included in this study through a systematic mobile app review (12 from Apple App Store and 11 from Google Play). Questions #15 and #16 of the Mobile App Rating Scale (MARS) was employed as a tool to quantitatively analyze the comprehensiveness and accuracy of the pharmaceutical content of the apps. All apps were reviewed based on a list of 26 DDI pairs (consisting of 20 true positive and six false positive examples) that are frequently reported within peer-reviewed literature for clinical information systems. The accuracy of DDI identification and comprehensive of the description were scaled to a range from one to five. **Primary Results:** MARS question #15 which assessed the accuracy of DDI information scored on average 2.9, while question #16, which measured the comprehensiveness of DDI description, scored 2.4 on average. Eleven (48%) of 23 apps scored four or higher for question #15, while seven (30%) apps scored less than one. DDI apps on average could only identify 58% (3/5) of the DDI pairs under study. **Principal Conclusions:** Results indicated that the pharmaceutical information being delivered by DDI mobile apps is inaccurate and potentially unsafe to consumers. To avoid any threat to the consumers' health, close monitoring of the mobile apps content is crucial.

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A physiologically-based approach to the pharmacokinetics of anti-TNF agents in pediatrics

PAUL RV MALIK[1,*], ANDREA N EDGINTON[1]

Background: Monoclonal antibodies (mAbs) against tumour necrosis factor (TNF) are used in children as young as two years old for treatment of autoimmune diseases. Little is known about how growth and maturation may impact the pharmacokinetics (PK) of these agents. With the same weight-based dose, young children (2-6 years) typically achieve lower exposures when compared to adults, while adolescents (12-18 years) do not. **Methods**: A physiologically-based pharmacokinetic (PBPK) model was developed in PK-Sim and Mobi (open-systems-pharmacology.com) to describe the subcutaneous absorption, distribution and elimination of anti-TNF mAbs in adults. The physiological parameters in the adult model were then adapted to create a pediatric model with anatomy and physiology according to known values in literature. Following evaluation of the pediatric model using observed pediatric PK data, sensitivity analyses were performed to identify the key physiological parameters in the pediatric model that were most influential for predicting exposure differences between adults and children. **Results**: The adult and pediatric PBPK models for anti-TNF mAbs adequately predicted the observed PK data and inter-individual variability. Sensitivity analyses suggest that the fast rate of subcutaneous absorption in children was driven by a fast lymph flow. Differences in distribution were related to differences in capillary surface area and leaky:tight tissue mass ratios. Low concentrations of the neonatal Fc receptor in the endothelium of young children were responsible for differences in elimination. **Conclusions**: A PBPK modelling approach to pediatric PK prediction for anti-TNF mAbs was demonstrated. Further research will be concerned with extrapolating the PBPK model to infants.

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The WAPPS-Hemo project: an innovative approach to individualized prophylaxis

ALANNA MCENENY-KING[1], *, PIERRE CHELLE[1], GARY FOSTER[2], ALFONSO IORIO[3,4]
ANDREA N EDGINTON[1]

The mainstay of severe hemophilia treatment is prophylactic replacement of the missing clotting factor (factor VIII for hemophilia A or IX for hemophilia B). Dosing regimen design is complicated by significant inter-individual variability in pharmacokinetic (PK) response that cannot be predicted by weight and age alone. Incorporation of the individual patient's PK profile by means of a population PK (PopPK) approach facilitates the adoption of dose tailoring into clinical practice. The WAPPS-Hemo program provides a web-accessible service to assess clinically relevant PK of factors VIII and IX. Using data from pharmaceutical companies and independent investigators, WAPPS-Hemo has generated the largest global repository of clotting factor PK data and this collection continues to grow through the contributions of the more than 100 co-investigator sites in the WAPPS-Hemo network. This unprecedented dataset has allowed for the development of generic (i.e. not brand-specific) PopPK models for conventional factor VIII, combining PK data from 8 brands into a single model. Body weight and age were found to be significant covariates on clearance and volume, as was brand of factor concentrate. This model has been mounted on the WAPPS-Hemo platform and is currently being used to produce estimates of individual PK parameters to guide dosing regimen design.

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Building bridges: how research changes in multi-disciplinary patient inclusive settings

KATHRYN MERCER[1,*], CATHERINE BURNS[2], LISA GUIRCUIS[3], JESSIE CHIN[2], JOYCE DOGBA[4] LISA DOLOVICH[5], LINE GUÉNETTE[6], LAURIE JENKINS[7], FRANCE LÉGARÉ[4], ANNETTE M[C]KINNON[9], JOSEPHINE M[C]MURRAY[10], KRYSTINE WAKED[1], KELLY GRINDROD[1,*]

Objective: To describe how engaging patients and other disciplines can change conclusions in qualitative health services research. **Approach**: A recent qualitative research project included a multi-disciplinary research team of health care professionals, engineers, information specialists, health systems specialists and patients. From this, two papers are being developed: 1) patient perspective on shared decision making; 2) healthcare professionals and health communication. Initial coding of patient and healthcare professional interviews was completed by the core research team. Then, a two-day research meeting with 11 multidisciplinary members of the research team, including a patient and a patient navigator, was organised to discuss and re-code data. Members coded four interviews individually prior to the meeting, and during the meeting placed and grouped them into emerging themes. **Results**: Initial coding led to five emerging themes on healthcare professionals, with the overall conclusion focusing on building electronic health records that facilitate care coordination. Group coding came to a slightly different conclusion: until pharmacists can see indications, and physicians gain insight into adherence, neither group will be fully able to provide the best care. Initial coding of patient interviews focused around how better tools are needed to facilitate the simplification of communicating health information and easing the burden on patients. After group coding, the conclusion ended very differently, centering around the influences on how decisions are made, with an emphasis on roles and power dynamics. **Conclusions**: More research needs to be done on how coding and conclusions change depending on who is included in the research team.

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Economic analysis of introducing community-pharmacist led influenza vaccine consultation service for Ontario seniors

GOKUL RAJ PULLAGURA[1,*], NANCY M WAITE[1], SHERILYN KD HOULE[1], WILLIAM WL WONG[1]

Objective: This study aimed to predict the relative quality of life changes, costs and cost-effectiveness of introducing a remunerated community-pharmacist led influenza vaccination consultation service for Ontario seniors in comparison to current practices. **Methods**: Using a cost-utility analysis through a public-payer perspective, the delivery of consultation services by community-pharmacists on influenza vaccine billable at $15, was compared to current standard practices (absence of standalone remunerated consultation services) over one influenza season. Base-case subjects included those aged ≥65 years accessing community pharmacy services. Data on vaccine safety and efficacy, transition probabilities, costs and utilities were primarily sourced from existing literature. In addition to the base-case, multiple deterministic and probabilistic sensitivity analyses were conducted using decision analysis software, TreeAge® Pro 2017. **Results**: The incremental costs per quality-adjusted life-year (QALY) gained for the comparator arm relative to the standard arm in the base-case was $993.64. The comparator arm was estimated to prevent 23 additional cases of severe influenza requiring hospitalization and 3,765 cases of mild influenza, not resulting in hospitalization or an out-patient physician visit over the standard arm. The interpretation of the base-case result was found to be robust across all sensitivity analyses. The analysis was mildly sensitive to age and vaccine uptake in the comparator arm. The projected additional costs of implementing pharmacist consultation services were estimated to be $1.47 million/year and the anticipated benefits included a gain of 1,232 QALYs/year over current practices. **Conclusion**: Introduction of standalone remunerated consultation services on influenza vaccination by community pharmacists for Ontario seniors offers a cost-effective alternative to current standard practices.

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Amyloid-β inhibitor drugs for Alzheimer's disease: from rational design to cell viability

MORGAN ROBINSON[1,2], JENNIFER LOU[3], ARVI RAUK[5], MICHAEL BEAZELY[1], ZOYA LEONENKO[2,3,4,*]

Alzheimer's disease (AD) is a devastating neurodegenerative disorder with no cures and limited treatment options. Amyloid-β (Aβ) accumulation is the definitive neuropathological hallmark of AD. Aβ aggregates to form neurotoxic oligomers that bind to nanoscale electrostatic and topographical features of the neuronal membrane; this disrupts membrane potential, neuronal function, and ultimately causes cell death. One potential strategy to prevent neurotoxicity associated with Aβ is to stabilize the non-toxic monomer, inhibiting the formation of toxic oligomers. Previously, SG pseudo-peptide aggregation inhibitors were rationally designed and optimized for affinity to Aβ using molecular dynamics simulations in Rauk's group. Next, in this work we experimentally tested lead candidates from these simulations using single-molecule force spectroscopy and metabolic cell viability assays. Here, we show on a single-molecule level that all SG inhibitors prevent dimerization of Aβ, shifting the distribution of Aβ binding forces in structurally unique fashion. Meanwhile, MTT assays demonstrate that two out of five SG inhibitors tested are non-toxic and can ameliorate Aβ toxicity to mHT22 cells. But, myristoyl-modified inhibitors exhibit dose dependent neurotoxicity to mHT22 cells alone. The results of these two studies, in combination with previously performed molecular dynamics simulations, indicate important structure-function relationships of effective peptide inhibitors for preventing Aβ toxicity. We show that SG inhibitors may be a promising preventative treatment for AD and should be pursued further in pre-clinical trials.

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Nanoparticles-coated intravaginal ring for dual delivery of siRNA and hydroxychloroquine against HIV infection

YANNICK TRAORE[1,*], YUFEI CHEN[2], EMMANUEL HO[1]

Purpose: Microbicides are an excellent alternative to condoms to help reduce transmission of human immunodeficiency virus (HIV). We propose to develop a segmented combination IVR whereby one-half of the IVR will be loaded with hydroxychloroquine (HCQ), to induce a quiescent state in T-cells and the other half will be coated with a pH-responsive film for the rapid release of small interfering RNA (siRNA)-encapsulated nanoparticles (siRNA-NP) targeting CCR5 gene, triggered by an increase in vaginal pH due to the presence of seminal fluid as a strategy for preventing HIV infection. **Methods**: Solid lipid nanoparticle made of glyceryl monosterate and L-α-phosphatidylcholine was used to encapsulate siRNA using double emulsion method, mixed with pH-sensitive polymer (Eudragit L100) and used to coat a matrix-type IVR segment, fabricated by injection molding from polyurethane. HCQ was loaded in a reservoir-type IVR segment. A release study was performed for each segment. The biocompatibility of the IVR was evaluated on cervicovaginal epithelial cell lines and on vaginal flora Lactobacilli. **Results**: IVR segments coated with a pH-sensitive polymer rapidly released fluorescent NP at pH8.2 (12.8 ± 1.7%) at 4 hours' time point but negligible amount at pH4.2 (0.26 ± 0.042%). The reservoir-type IVR segment containing HCQ continuously released drug up to 21 days with a near zero-order release profile (R2 value =0.99) with a mean daily release of 17.01 ± 3.6 μg/mL. The IVR segments were not toxic to the vaginal cells or microflora. **Conclusion**: We describe an IVR system capable of controlled release of HCQ and also siRNA-NP at high pH and non-cytotoxic towards lactobacilli and vaginal/cervical epithelial cells.

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RESEARCH ABSTRACTS

POSTER PRESENTATIONS

Single-step green synthesis of gold nanoparticles functionalized with green tea extract

MOHAMED ABORIG[1], SHRUTI NAMBIAR[1,2,3], ERNEST OSEI[3,4,5], ANDRE FLECK[3,6], JOHNSON DARKO[3,5,6], ANTHONY J MUTSAERS[6], SHAWN WETTIG[1,2]

Gold nanoparticles (AuNPs) have been widely studied for several biomedical applications including drug delivery, radiosensitization, and in diagnostics as image contrast agents. In this study, we propose a simple and reliable method for synthesis of stable colloidal solution of AuNPs capped with epigallocatechin-gallate (EGCG), a potent phytochemical from green tea, that has been shown to have anti-cancer properties. AuNPs were synthesized via reduction of gold precursor, chloroauric acid (HAuCl4), using solubilized EGCG which plays the dual role of a reducing agent and stabilizing agent. The sample was then dialyzed for >21 hours to remove any unreacted ions. The formation of AuNPs was first confirmed with the appearance of ruby red colour. The EGCG-AuNPs were characterized using ultraviolet-visible (UV-vis) spectroscopy, dynamic light scattering (DLS), transmission electron microscopy (TEM), and inductively coupled plasma emission spectroscopy (ICP-OES). UV-vis data showed a single absorption peak at 525 nm confirming the formation of AuNPs. The DLS measurements showed a single intensity peak with an average particle size of 26.88 ± 0.2 nm and an average polydispersity index of 0.188 ± 0.006. The samples were found to be stable for 1, 7, and 21 d after synthesis. The morphology of the EGCG-AuNPs, inspected using TEM, was found to be mostly spherical. ICP-OES data indicates that the average AuNP concentration obtained from the synthesis is 416.9 ± 19 μg/mL. In conclusion, we report a one-step green process for synthesis of stable and monodisperse EGCG-AuNPs.

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Marijuana smoke induced-airway epithelial barrier dysfunction and pro-inflammatory cytokine production is inhibited by LABA/GCS intervention in vitro

JENNIFER AGUIAR[1,*], RYAN D HUFF[2], JONATHAN PAGE[3], ANDREW C DOXEY[1], JEREMY A HIROTA[4]

Marijuana is used by ~22.2 million people every month in the United States, a number that is expected to rise as more states legalize recreational use. Although previous studies have indicated a link to increased risk of bronchitis, marijuana smoke-induced immune responses in lung epithelial cells remain poorly understood. Furthermore, the efficacy of standard combination inhaled long-acting β2-adrenoceptor agonist (LABA) and glucocorticoids (GCS) therapy on marijuana smoke-induced responses remains unknown. We developed an in vitro marijuana smoke extract (MSE) exposure model based on current published cigarette smoke extract (CSE) models. Tobacco and marijuana cigarettes were smoked into 4mL of culture medium, filtered and standardized to reach a 10% dose. Calu-3 cells were cultured and apically exposed to vehicle, MSE, or CSE with and without an intervention of budesonide (100nM) and formoterol (10nM) for 24 hours. Apical supernatants were collected for multiplex cytokine quantitation. Transepithelial Electrical Resistance (TEER) was measured pre- and post-exposure. Exposure of Calu-3 cells to CSE and MSE impaired TEER compared to unexposed cells by 21.5% (P<0.0001) and 15.7% (P<0.0005), respectively. LABA/GCS intervention prevented decreases in TEER in both CSE (+3.9%) and MSE (+14.2%, P<0.0014) conditions. Significant increases in IL-8 and IL-6 were observed in cells exposed to CSE or MSE, but levels were attenuated with LABA/GCS intervention. Our work shows that marijuana smoke impairs epithelial cell barrier function similarly to cigarette smoke. Both smoke extracts induce pro-inflammatory cytokines that are attenuated with LABA/GCS therapy. LABA/GCS therapies may be useful to regulate lung inflammation in medicinal marijuana users.

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Visible minority patients' perceptions of bias in community pharmacy services

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Background: Health disparities among minority patients are well-documented and recognized as serious issues in the Canadian healthcare system. While a growing body of research examines the patient-doctor relationship and its influence on health disparities, few studies have examined pharmacists and their relationships to patients. **Objective**: To gain a better understanding of Visible Minority patients experiences with Ontario community pharmacists services. **Method**: A semi-structured interview questionnaire will develop, pilot test, and revise using several pharmacists. The questionnaire will use to conduct face-to-face patient interviews in Kitchener-Waterloo reign. English-speaking patients who have used pharmacist services within the past three years will be included in this study. Patient interviews will be conducted by the primary researcher, audio-recorded, and transcribed verbatim. The interview transcripts will be analyzed. **Implications**: As Canada becomes a more diverse nation and as health care providers, including a pharmacist, strive to eliminate health care disparities, issues of bias, attitude needs to be addressed. Furthermore, an indirect benefit will come from being able to better understand and gain insight into Visible Minority patients' perspective opinions, attitude about pharmacists and pharmacy services.

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A cost-effectiveness analysis comparing two follow-up strategies to detect relapse in diffuse large B-cell lymphoma patients: CT scan surveillance imaging and symptom presentation

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Background: Routine surveillance imaging using CT scans is a widely debated follow-up strategy for diffuse large B-cell lymphoma patients in complete remission. There are benefits and risks associated with this practice and it is unclear whether routine surveillance imaging is cost-effective. This analysis compared two follow-up strategies for detecting relapse: routine CT scan imaging in asymptomatic patients, and follow-up during which patients presented with clinical symptoms of relapse. **Methods**: A cost-utility analysis was performed using a Markov economic model to assess the incremental cost-effectiveness ratio (ICER) per quality adjusted life year (QALY) gained from routine surveillance imaging compared to clinical presentation of symptoms. The analysis was from a public payer perspective and used a willingness-to-pay-threshold of $100,000. Outcomes measured included transition probabilities, utilities, costs and ICERs. Additional scenario and sensitivity analyses were also conducted. It was assumed that 26% of patients were asymptomatic and could benefit from this practice and 74% were symptomatic, and that CT scans led to a reduction of risk of death from lymphoma by 13%. **Primary results:** Routine surveillance imaging was not cost-effective. The analysis showed that routine CT scans are more costly and less effective than follow-up without imaging. To calibrate the model, the percentage of patients who could benefit from CT scans and the reduction of risk from lymphoma were varied from 0 to 100%, and the conclusion remained the same. **Conclusions**: Routine surveillance imaging with CT scans should not be recommended as a follow-up strategy because it offers no added clinical utility.

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A spatial, long term-potentiation expression gradient within the CA1 stratum radiatum

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Long-term potentiation (LTP) is the most widely studied model of synaptic plasticity, and is widely regarded as a critical cellular mechanism underlying learning and memory. For several decades, a large proportion of LTP experiments have taken advantage of the conserved neurocircuitry within the acutely prepared hippocampal slice; in particular, these studies have stimulated the Schaffer collateral and measured responses throughout the CA1 stratum radiatum. However, a large variation in magnitude of LTP recorded exists in the literature, which makes cross study comparisons challenging. One possible reason for the variation observed across earlier studies may be the lack of precision regarding the positioning of the stimulating and recording electrodes in these reports. Hence, we investigated the magnitude of LTP expression within the CA1 stratum radiatum of acute hippocampal slices with respect to the distance between the recording position and pyramidal soma. Using a multi-electrode array recording system, we were able to precisely record LTP expression at a 100 μm, 200 μm, and 300 μm distance away from the pyramidal soma within the stratum radiatum. LTP was induced by two tetani (100 Hz) with an inter-stimulus duration of 20 seconds. Preliminary results show that a clear spatial plasticity gradient can be observed within the stratum radiatum of the CA1 region. More specifically, the greatest LTP expression was seen at those points 100 μm from pyramidal soma. Our results indicate that LTP is not homogeneously expressed within the CA1 stratum radiatum, and suggest the importance of precisely documenting recording position in LTP experiments.

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Investigating the correlation between miscibility and physical stability of solid phospholipid dispersions using fluorescence-based techniques

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Amorphous solid phospholipid dispersion (SPD) has been widely used to enhance the bioavailability of water-insoluble drugs, since amorphous drug has higher solubility and faster dissolution as compared with its crystalline counterpart due to high free energy. However, amorphous drugs tend to recrystallize in SPD with time, negating the desired enhancement on dissolution. Also, it is challenging to evaluate drug-phospholipid miscibility although various techniques have been used for this purpose. Therefore, the objective of this study was to investigate the feasibility of fluorescence-based techniques to assess the drug-phospholipid miscibility, and to probe the correlation between miscibility and physical stability. The miscibility of indomethacin-phospholipid (IDM-PL) system was characterized by infrared (IR) spectroscopy, fluorescence spectroscopy and fluorescence microscopy. Double emission peaks were observed in the fluorescence spectra of high drug-loading samples, suggesting the existence of two polarity environments. Phase transformation of IDM-PL stored at 40℃ was confirmed by fluorescence imaging. The experimentally determined drug loading limit of IDM-PL system was 30%, above which amorphous-amorphous phase separation was thermodynamically favored, leading to the recrystallization in the drug-rich phase as depicted in the fluorescence images. The results showed good correspondence to IR, and further confirmed the phase transformation suggested by conventional technique. In conclusion, fluorescence techniques were successfully used to evaluate drug-phospholipid miscibility for the first time. The miscibility and physical stability of IDM-PL system could be determined, visualized and correlated by proposed method. Fluorescence techniques show promise in the evaluation of interactions between autofluorescent drugs and phospholipids.

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Understanding the interactions between Pluronics® and DPPC-CHOL model membrane: Langmuir monoloayer and Brewster's angle microscopy studies

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Amphiphilic Pluronics block copolymers are widely used as an adjuvant polymer to improve non-viral gene transfection efficiency. Adding Pluronics to the gene delivery system promotes micelle formation which protects the non-viral vector from degradation and increases its circulation time in the body. The ability of non-viral vectors to disrupt biological membranes is crucial for effective gene delivery, however, the interactions that occur between Pluronics and biological membranes are not fully understood. In this project, the nature of the interactions between four Pluronics (L44, F87, P103, and F108) and a model membrane (DPPC-CHOL) at the air–water interface was studied using Langmuir monolayer methods and Brewster's angle microscopy (BAM). The resulting surface pressure–molecular area isotherms and corresponding BAM images indicate that the Pluronics strongly interact with the model membrane at low surface pressure (~ 0-5 mN/m). At 30 mN/m, the surface pressure of real biological membranes, the Pluronics fluidize the model membrane which is indicated by a decrease in the compressibility modulus of the DPPC-CHOL model membrane from 188 mN/m in the absence of the Pluronics to approximately 80-90 mN/m when treated with each of the Pluronics studied. These results demonstrate that Pluronics effectively interact with a model biological membrane and induce its fluidization which suggests that incorporation of these Pluronics in non-viral gene delivery systems will lead to more efficient transfection.

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Effect of somatostatin and its derivatives on amyloid proteins

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An age-related neurodegenerative disorder - Alzheimer's disease (AD), the most prevalent cause of dementia, is characterized by the extensive disposition of both amyloid-beta (Aβ) plaques and neurofibrillary tangles (NFTs) in the brain. The progressive memory deficits and other disturbances in Alzheimer's patients' daily activities have often been observed and associated with significant social burden, eventually leading to the increase of morbidity and mortality. Because of the modest benefit effects of the currently available cholinesterase inhibitors and NMDA-receptor antagonist, our investigation came in to study the direct interaction of a peptide hormone somatostatin (SST) and its derivatives (D-Trp8-somatostatin, octreotide and lanreotide) with Aβ peptide. The aggregation kinetics in the presence and absence of Aβ by SST and its derivatives were evaluated using the thioflavin T (ThT)-based fluorescence spectroscopy. The Aβ peptide aggregation morphology in the presence and absence of SST derivatives was monitored using transmission electron microscopy (TEM), and the binding interactions were investigated by the computational studies. These results demonstrate that SST and its derivatives are potential Aβ aggregation inhibitors. Particularly, SST was identified as the most potent Aβ inhibitor.

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Cost-effectiveness of tenofovir alafenamide in the treatment of HBeAg-positive chronic hepatitis B

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Background: Tenofovir alafenamide (TAF) has received approval for the treatment of chronic hepatitis B (CHB) in Canada, and its cost-effectiveness remains unknown. Objective: The aim of this study was to build a model and evaluate the cost-effectiveness of TAF versus other treatments on HBeAg-positive CHB patients from a Canadian payer perspective. **Methods**: A Markov model based on the published literature and an unpublished systematic review and meta-analysis was developed to compare the cost-effectiveness of four CHB treating strategies: lamivudine (LAM), entecavir (ETV), tenofovir disoproxil fumarate (TDF), and TAF for 20-65 years old individuals with HBeAg-positive noncirrhotic CHB. The model adopted a time horizon of lifetime, and outcomes measured were costs (2017 Canadian dollars), quality-adjusted life years (QALYs), and incremental cost-effectiveness ratios (ICERs). Results: At an annual cost of $107 930, TDF generated 25.77 QALYs per person, with an ICER of $5 727.10/QALY referencing LAM. At an additional cost of $8 627.11, TAF generated an additional 0.36 QALYs, with an ICER of $23 956.85/QALY referencing TDF. ETV was found to be more expensive and less effective than TDF. The results were sensitive to the HBeAg seroconversion rate of the treatments and treatment starting age. **Conclusions**: TAF is the most cost-effective treatment for HBeAg-positive CHB patients in Canada, and ETV is unlikely to be an optimal strategy for treating HBeAg-positive CHB.

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Pharmacokinetic (PK) dose prediction for switching from short-acting to long-acting factor VIII (FVIII) concentrates in persons with hemophilia A

JACKY YU[1], ANDREA EDGINTON[1]

Hemophilia A is a bleeding disorder in which the blood is unable to form clots due to a lack of clotting FVIII. Standard treatment for the prevention of bleeds is prophylactic entailing FVIII infusions to replenish this missing factor in the body. In clinical pharmacy practice, there are numerous FVIII concentrates available for patients, although switching products may be warranted due to side effects or hypersensitivity.[1] The FVIII dose of an individual is varied between concentrates due to differences in the PK profile, which poses problems when determining optimal dosing regimens.[2] The objective of this research is to quantify the population percentile in PK parameter estimates for an individual taking short-acting FVIII concentrate, and to assess its predictability when switching to a long-acting FVIII product. PK data on individuals who have switched from short to long-acting FVIII will be taken from the Web-Accessible Population Pharmacokinetic Service – Hemophilia (WAPPS-Hemo.org) and from data gifted by the industry. Individual PK parameters of clearance, volume of distribution, half-life and time-to-2% will be estimated using population PK models built into WAPPS along with Bayesian forecasting. Individual PK parameters of short and long-acting FVIII will be assessed using quantile-quantile plots to compare the percentiles in which the individual falls within the larger population. Assessing percentile correlations will allow for PK parameter predictions for long-acting FVIII products during switching and subsequently lead to optimal FVIII dosing, resulting in safer and cost-effective changes in clinical practice.

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Model Qualification of PK-Sim® in extrapolating pharmacokinetic parameters in pediatric patients

YEJIN YUN[1], ANDREA EDGINTON[1]

Background: Several methods for extrapolating the dose-exposure relationship from adults to children have been developed and are based on knowledge of how growth and/or maturation affect this relationship. Physiologically based pharmacokinetic (PBPK) modeling is one such method where virtual children are built based on known trajectories of anatomy and physiology across age and drugs are defined by physicochemical properties. These models have been used to derive doses for pediatric clinical trials and to assess risk of exposure to environmental chemicals. However, the assessment criteria for pediatric PBPK model quality have not yet been established. The objective is to evaluate the predictive capacity of the pediatric PBPK modeling platform PK-Sim®. **Methods**: Using a well developed pediatric PBPK modeling workflow [1], PBPK models in adults were constructed for several compounds (grouped by major clearance process e.g. CYP3A4). Several age groups of virtual pediatric individuals (n=100) were created to represent children in pediatric clinical studies. The mean and variance of simulated PK parameters from virtual populations were compared to observed values. The pediatric PBPK model was considered qualified for a major clearance process when two or more compounds described the observed data within a 2-fold deviation. **Results:** Model qualification is ongoing with preliminary modeling for theophylline (i.e. CYP1A2 substrate) demonstrating that the mean ratios of predicted vs. observed values of clearance and volume of distribution are (1.0-1.4) and (0.48-0.79), respectively. **Conclusion:** Predictive accuracy of PBPK modeling will increase confidence in its use for first-in-children dose selection and risk assessment in the pediatric population.

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