NUS National University of Singapore | Department of Pharmacy
Faculty of Science

AY1920 Semester 2
Postgraduate Seminar
24 February 2020
S4 Level 2, PPS Hub
9.00 am - 3.00 pm

Program

0900 - 0910	Opening Address (Prof Eric Chan)
0915 - 0945	Ms Eleanor Cheong
0945 - 1015	Ms Wang Yali
1015 - 1030	Break
1030 - 1100	Ms Valerie Sin
1100 - 1130	Ms Vanitha Selvarajan
1130 - 1230	Lunch Break
1230 - 1300	Ms Mohua Das
1300 - 1330	Mr Lee Choon Keong
1330 - 1345	Break
1345 - 1415	Mr Ramy Elsergany
1415 - 1445	Ms Cheryl Wong
1445	Closing Remarks & End

ALL ARE WELCOME

*** mandatory for all PG students**

Systematic Development and Verification of A Physiologically-Based Pharmacokinetic Model of Rivaroxaban

Ms Eleanor Cheong
Supervisor: Prof Eric Chan

ABSTRACT Rivaroxaban is indicated for stroke prevention in nonvalvular atrial fibrillation and has recently emerged as an alternative treatment for venous thromboembolism in patients with cancer. Its unique dual mode of elimination, comprising CYP3A4/2J2-mediated hepatic metabolism and P-glycoprotein (P-gp)-mediated renal secretion, renders rivaroxaban susceptible to both intrinsic and extrinsic variabilities that in turn implicate bleeding risks. Upon robust model verification, physiologically-based pharmacokinetic (PBPK) models are qualified for the quantitative rationalization of complex drug-drug-disease interactions (DDDIs). In this study, development of a PBPK model of rivaroxaban, with the inclusion of a mechanistic kidney component, first provided insight into the previously arcane role of basolateral organic anion transporter 3 (OAT3)-mediated proximal tubular uptake in influencing the renal elimination of rivaroxaban in both healthy and renal impaired patients. Retrospective DDI simulations linking rivaroxaban with prototypical CYP3A4/2J2 and P-gp inhibitors (verapamil and ketoconazole) further demonstrated how significant transporter-mediated DDIs were predicated on concurrent basolateral OAT3 and apical P-gp inhibition. In conclusion, our developed PBPK model is systematically verified for the prospective interrogation and management of untested, albeit clinically relevant DDDIs pertinent to the use of rivaroxaban.

BIOGRAPHY Eleanor Cheong graduated from the National University of Singapore in 2015 with a BSc (Pharmacy) (Hons). She is currently pursuing her PhD degree under the supervision of Professor Eric Chan in the Department of Pharmacy, National University of Singapore. Eleanor's academic research focuses on the optimization of pharmacotherapy in both cardiology and prostate oncology. She is working on utilizing bottom-up physiologically-based pharmacokinetic modeling incorporating in vitro data to mechanistically quantify complex albeit untested drug-drug-disease interactions involving direct oral anticoagulant, rivaroxaban. Additionally, she is also interested in investigating how the highly variable pharmacokinetics of steroidogenic CYP17A1 inhibitor abiraterone may influence target exposure, drug-target binding and ultimately therapeutic efficacy.

TCM-ID database: Bioinformatics-enhanced traditional Chinese medicine data source

Ms Wang Yali
Supervisor: Prof Chen Yu Zong

ABSTRACT Traditional Chinese medicine (TCM) has been widely used by ethnic populations. Its claims, clinical effectiveness, mechanisms, and drug discovery potentials are under investigations. These investigations may be facilitated by bioinformatic analysis of the TCM putative targets, which have primarily been determined by *in-vitro* and i*n-silico* studies. There is a need for uncovering clinically-relevant targets. Because target expression in the patients is a pre-requisite for any claimed TCM therapeutics, a step towards the uncovering of clinically-relevant targets is by analysing their expressions in the big patient data. So, the gene expression of literature-reported experimental targets of TCM prescriptions by hierarchical clustering method were profiled. The target gene expression heatmaps of TCM prescriptions are provided in the TCM-ID database as a bioinformatics-enhanced TCM data source.

BIOGRAPHY Wang Yali received her M.Sc. degree from Department of Pharmacy, Sun Yat-sen University, China. Currently, she is a PhD candidate in the BIDD (Bioinformatics and Drug Design) group under Professor Chen Yu Zong. Her work involves update of the traditional Chinese medicine database TCM-ID, statistical analysis and case studies of the target gene expression heatmaps of TCM prescriptions in order to lay the foundation of uncovering clinically relevant targets, and development of machine learning models to predict pharmaceutical properties of small molecules.

Utilising Phosphodiesterase Type 5 (PDE-5)-Cyclic Guanosine Monophosphate (cGMP) Dependent Protein Kinase G (PKG) Complex for Discovery of PDE-5 inhibitors

Ms Sin Jia En Valerie
Supervisor: A/Prof Koh Hwee Ling

ABSTRACT Erectile dysfunction is a common clinical problem affecting males of all ages, where recent longitudinal studies have shown that the incidence is between 32%-80%. It is often treated with Phosphodiesterase Type 5 (PDE-5) inhibitors such as Sildenafil. However, limitations of current PDE-5 screening methods and low selectivity of PDE-5 inhibitors underscore the need for a more specific screening method. The interaction of PDEs with specific receptors for cyclic nucleotides and cyclases has been shown to play an important role in the regulation of various cellular functions. In this study, a fluorescence polarisation (FP)-based screening assay was developed for the discovery of inhibitors. The composite active site formed from complexation of PKG with PDE5 is highly specific and thus represents a better target than free diffusing PDEs for the discovery of more specific PDE5 inhibitors. A pilot screening of several plant extracts and fractions was also conducted.

BIOGRAPHY Sin Jia En Valerie graduated from Department of Pharmacy, Faculty of Science, National University of Singapore with a BSc (Pharmacy) (Hons.) degree. She is currently pursuing her PhD under the supervision of A/Prof Koh Hwee Ling and co-supervision of A/Prof Ganesh Srinivasan Anand. Her research interest lies in the drug discovery from medicinal plants, focusing on phosphodiesterase (PDE) inhibitors. Her work involves characterization and isolation of active phytoconstituents through bioassay guided fractionation. Other interests include assay development using fluorescence polarization and the use of amide hydrogen/deuterium exchange mass spectrometry (HDX-MS) as a tool for understanding protein dynamics.

Stapled β-hairpin AMP: Impact of staple length, position and number on antimicrobial activity and stability

Ms Vanitha Selvarajan
Supervisor: A/Prof Rachel Ee

ABSTRACT Hydrocarbon stapling of peptides involves a ring-closing metathesis reaction between two Cα-alkenyl amino acids incorporated into the peptide sequence. This technique, commonly employed on α-helical peptides, has shown increased proteolytic resistance and penetration efficacy. However, impact of stapling on β-hairpin peptides has not yet been explored. In this study, we have created a library of hydrocarbon stapled β-hairpin peptides with variations in staple length, position and number and further evaluated the impact of the modifications on peptide stability and activity against Gram-negative bacteria. Of interest, although double-stapling aided the peptides in retaining its secondary structure, the apparent increase in the rigidity significantly affected their antimicrobial activity. Evidently, those stapled peptides with the better stability and activity profile were also able to effectively kill multiple clinical resistant pathogens. We further studied the mechanism of action of the most effective peptide using various imaging techniques. Overall, we found that systematic positioning of staples across β-hairpin peptides is advantageous in manipulating the activity of the peptides while tuning their stability which is critical for the future clinical translation of antimicrobial peptides (AMP).

BIOGRAPHY Vanitha received her BTech in Biotechnology from Anna University, India in 2013 and MTech in Biotechnology from Indian Institute of Technology Guwahati, India in 2015. She started working as a senior research fellow at the Indian Veterinary Research Institute in 2016. She is currently pursuing her PhD under the supervision of Associate Professor Rachel Ee Pui Lai. Her research predominantly focuses on developing novel treatment strategies against Gram-negative pathogens.

Studies towards the development of epigenetic probes for the mammalian AlkB family of nucleic acid demethylases

Ms Mohua Das
Supervisor: Asst Prof Esther Woon

ABSTRACT The mammalian AlkB family consists of nine enzymes, namely ALKBH1-8 and FTO. They catalyse epigenetic modifications in nucleic acids and histones with differing substrate and nucleotide specificities. Owing to their diverse catalytic specificities, the AlkB family has been involved with a range of physiological or pathological roles. As a result, there is a keen interest in developing potent small-molecule probes to understand their functional and molecular mechanisms better. This thesis work involves studying different approaches to develop small molecule probes targeting the AlkB enzymes. In the current approach, we aim to explore the lesser-studied ALKBH1 for potent inhibition. Literature studies on ALKBH1 suggest that its structure and catalytic substrates are still unclear. To accomplish our aim, we have established an in vitro inhibition assay and developed a 3D model of ALKBH1. We are further using this model for structure-based probe design to predict scaffolds that bind with high affinity to ALKBH1.

BIOGRAPHY Mohua had graduated in 2013 with a B.Pharm degree in Pharmaceutical Sciences from the West Bengal University of Technology, India. Subsequently, she had pursued M.S.Pharm in Natural Products from the National Institute of Pharmaceutical Education and Research (NIPER), where she had worked on azomethine ylide cycloaddition on Curcumin for her Master's thesis. She had also worked as a Chemist under the Ministry of Health and Family Welfare, India before joining her doctoral studies in Singapore, where she was involved in the testing and quality control of imported drugs available in India. At present, she is doing her doctoral studies in Medicinal Chemistry at the Department of Pharmacy, National University of Singapore under the supervision of Assistant Professor Esther Woon. Her research interests focus on understanding the chemical biology and development of small-molecule probes to target the AlkB family of nucleic acid demethylases.

Proniosome gel for dermal delivery of anti-inflammatory compound for osteoarthritis

Mr Lee Choon Keong
Supervisor: A/Prof Giorgia Pastorin

ABSTRACT Dermal delivery of bioactive molecules remains an attractive route of administration due to enhanced accumulation of bioactive molecules at the site of application while reducing the systemic side effects. Proniosome gel can be a suitable dermal delivery system due to the presence of non-ionic surfactants acting as a chemical penetration enhancer (CPE). In exploiting the CPE, sufficient amount of bioactive molecules should be released from the formulation and this can be achieved by reducing the stiffness and enhancing the hydrating ability of the proniosome gel. Using berberine as a model compound, we demonstrated that by incorporating Span 80 and Tween 20 into Span 60-based proniosome gel, it enhanced the release of berberine from the formulation in an ex-vivo skin permeation study. This result translates into higher suppression of pain observed in an in-vivo mice osteoarthritis model. Thus, this demonstrates the feasibility of using proniosome gel as a dermal delivery platform.

BIOGRAPHY Choon Keong graduated from Nanyang Technological University, Singapore with a B.Sc (Hons) in Chemistry & Biological Chemistry. He is pursuing his Ph.D under the supervision of A/P Giorgia Pastorin. His current research focus on dermal delivery of anti-inflammatory compounds for osteoarthritis and have experience in working on cell-derived nanoparticles for anti-cancer therapy.

Influence of the surface tension of wet massing liquid on the functionality of microcrystalline cellulose as pelletization aid

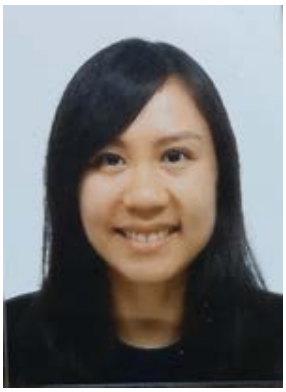
Mr Ramy Elsergany
Supervisor: A/Prof Paul Heng

ABSTRACT Microcrystalline cellulose (MCC) is the gold standard pelletization aid. This study was designed to investigate the impact of surface tension of moistening liquid on the functionality of MCC as pelletization aid. For this purpose, sodium dodecyl sulfate (SDS), poloxamer 188 (PL), di-potassium hydrogen phosphate (K_2HPO_4) and combinations thereof were incorporated into the powder blend comprised of MCC and dicalcium phosphate (DCP) at different levels. Physical mixture (PM) and co-processed composite (Cop) of MCC and sodium carboxymethyl cellulose (SCMC) replaced MCC as pelletization aids. The pellets prepared were characterized for their median diameter (D_{50}), particle size distribution (PSD), sphericity, porosity, tensile strength and disintegration. SDS induced a drop in the surface tension of water from 68.7 to 23.7 mN/m at 0.25 % (w/w). In contrast, the surface tension values of PL and K_2HPO_4 solutions were 2.08- and 3.07-fold higher than that of SDS solutions, respectively. MCC based pellets obtained with SDS showed wider PSD and lower sphericity than those made with PL, K_2HPO_4 and their combinations. In addition, the PSD and porosity increased with rise of SDS concentration from 0.05 to 0.25 % (w/w). Pearson's correlation analysis revealed an inverse relationship between porosity and tensile strength for these pellets. It was thus inferred that a critical surface tension of moistening liquid was essential to be effective for pelletizing ability with MCC. Replacing MCC with PM or Cop as pelletization aids guaranteed the pelletizing ability even with high concentrations of SDS. The most distinguished differences between pellets based on MCC, PM and Cop are sphericity and disintegration. PM and Cop based pellets were less spherical and able to disintegrate.

BIOGRAPHY Ramy Elsergany received his B.Sc. (Pharmacy) in 2008 from Faculty of Pharmacy, Tanta University (TU), Egypt. After graduation, he got his Master's degree at Department of Pharmaceutics and Biopharmaceutics, TU, and published one article in one of the international peer reviewed journals. Ramy has very good industrial experience as he worked as R&D pharmacist at Sigma Pharmaceutical Industries for more than four years. In addition, Ramy was assistant lecturer of Pharmaceutics and Biopharmaceutics at DUST University (Egypt) for more than two years before receiving his PhD scholarship. Currently, Ramy is pursuing his PhD under the supervision of A/Prof Paul Heng. His current research focuses on multiple unit-pellet systems (MUPS). During his PhD candidature, Ramy received internship at Institute of Pharmaceutics and Biopharmaceutics, Heinrich Heine University, Germany, where he joined Pharmaceutical Solid State Research Cluster (PSSRC).

Development of Eudragit Nanoparticulate Formulation of Paclitaxel for the Treatment of Drug-Resistant Cancer due to P-glycoprotein (Pgp) Overexpression

Ms Cheryl Wong
Supervisor: A/Prof Gigi Chiu



ABSTRACT Paclitaxel is an effective chemotherapy agent that is approved to treat various kinds of cancer. However, its use is limited by severe hypersensitivity reactions as it is formulated in Cremophor EL to overcome its low water solubility. Furthermore, cancer cells have been observed to develop resistance to paclitaxel. One common mechanism for resistance is the overexpression of P-glycoprotein (P-gp) on cancer cells, which actively pumps the drug out of cancer cells. Pluronic 85 (P85) has been shown to inhibit P-gp efflux. This study sets to develop Eudragit and P85 nanoparticles to load paclitaxel, with the aim of 1) Improving solubility of paclitaxel without the use of Cremophor EL, thus reducing toxicity of the formulation and 2) Overcome P-gp efflux of paclitaxel in multidrug resistant cancer cells. The preparation and functional evaluation of nanoparticles on cells overexpressing P-gp will be discussed.

BIOGRAPHY Cheryl graduated with a Bachelor of Science (Pharmacy) (Hons.) degree from the National University of Singapore in 2013, and practised as a pharmacist at Khoo Teck Puat Hospital until 2016. She is currently pursuing her Ph.D. under the supervision of A/P Gigi Chiu. Her present research interests focus on the development of Eudragit-based drug delivery systems and nanoparticulate-formulations.