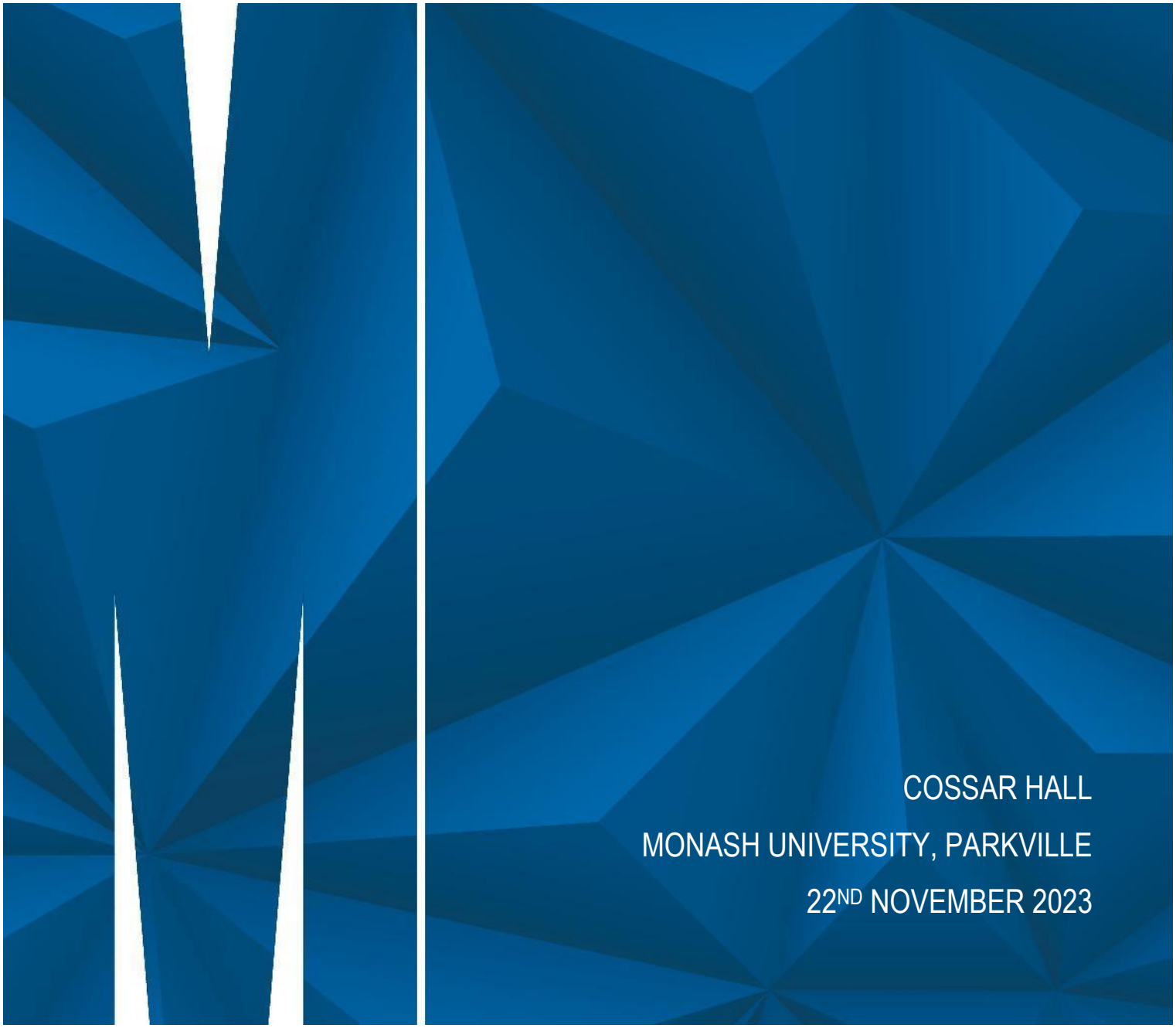
MONASH University

PARKVILLE POSTGRADUATE ASSOCIATION

PHARMACY AND PHARMACEUTICAL SCIENCES

18TH ANNUAL HIGHER DEGREE BY RESEARCH (HDR) SYMPOSIUM



COSSAR HALL

MONASH UNIVERSITY, PARKVILLE

22ND NOVEMBER 2023

Monash University and the Parkville Postgraduate Association (PPA) gratefully acknowledge the support of the following companies and organisations:

CONTENTS

ABBREVIATIONS

CMUS	Centre for Medicine Use and Safety
DDB	Drug Discovery Biology
D4	Drug Delivery, Disposition, and Dynamics
MedChem	Medicinal Chemistry
PPSEd	Pharmacy and Pharmaceutical Sciences Education

SYMPOSIUM PROGRAM

Registration	SISSONS BUILDING FOYER
8.00 - 8.45 am	**Registration**
Opening Ceremony	LECTURE THEATRE 5
8.45 - 9.00 am	**Symposium Opening**
9.00 - 9.55 am	**Keynote Plenary** Curiosity and Empathy - An antidote to “Lost in Translation”? ***Dr Craig Rayner*** *(Director, Regional centre for respiratory medicine and tropical diseases, Moderna)*
Oral Presentation Session 1 *Chairs: Amelia Miklavec, Showmika Supti*	LECTURE THEATRE 5
10.05 - 10.20 am	Advanced materials to treat organ failure via inhibition of pancreatic enzymes in the gut ***Zijun Lu*** *(D4)*
10.20 - 10.35 am	Tree-based scan statistics: real-world data mining to identify drug repurposing signals ***George Tan Shao Qian*** *(CMUS)*
10.35 - 10.50 am	Biased Agonism of Formyl Peptide Receptor 2 Governs Its signaling and trafficking profile ***Cheng (Selena) Peng*** *(DDB)*
10.50 - 11.05 am	Targeting redox processes to treat drug-resistant malaria parasites ***Annie Roys*** *(D4)*
Morning Tea & Poster Viewing	COSSAR HALL
11.05 - 11.50 am	**Morning Tea & Poster Viewing**
Poster Presentation Session 1: Group A *(concurrent)*	COSSAR HALL
11.10 - 11.15 am	Naphthalimides: A Novel Scaffold for Sensing the Micro-Environment of Amyloids ***Kai Kikuchi*** *(MedChem)*
11.15 - 11.20 am	Top 10 signs and symptoms of psychotropic adverse events to be monitored in nursing home residents ***Brigid McInerney*** *(CMUS)*
11.20 - 11.25 am	Development of Dual-Functionalized Fluorophores to Monitor Antibody-Drug Conjugates ***Tracey Luu*** *(MedChem)*
11.25 - 11.30 am	Lipid-dependent activation of the orphan G protein-coupled receptor, GPR3 ***Isabella C Russell*** *(DDB)*
11.30 - 11.35 am	Dual BET and PI3K inhibitors for the treatment of T-cell non-Hodgkin Lymphoma ***Jackson He*** *(MedChem)*
11.35 - 11.40 am	Modulation of microglial fatty acid binding protein 4 to reduce neuroinflammation in MND. ***Amelia Miklavec*** *(D4)*
11.40 - 11.45 am	Exploration of Phenoxazine Derivatives for the Treatment of Tuberculosis ***Eric Toan Le Tran*** *(MedChem)*
Poster Presentation Session 1: Group B *(concurrent)*	COSSAR HALL
11.10 - 11.15 am	Design and Synthesis of Covalently Tethered Asymmetric Tetrameric Cyclic Peptide Nanotubes ***William Parsons*** *(MedChem)*
11.15 - 11.20 am	Quality of medicines for the management of hypertensive disorders of pregnancy: a systematic review ***Pooja Maharjan*** *(D4)*
11.20 - 11.25 am	Is remoteness associated with secondary prevention medications post STEMI? ***Adam Livori*** *(CMUS)*
11.25 - 11.30 am	Potent and irresistible bis-1,2,4-triazines likely target the parasite nucleus ***Annie Luo*** *(D4)*

11.30 - 11.35 am	Developing Allosteric Ligands of the Metabotropic Glutamate Receptor Subtype 5 as CNS therapeutics ***Scott Wong*** *(MedChem)*
11.35 - 11.40 am	siRNA Delivery using Polymer-Grafted Porous Silicon Nanoparticles ***Zahra Abousalman Rezvani*** *(D4)*
11.45 - 11.50 am	Exploring PfExportin-1 as a Novel Antimalarial Target via Nuclear Fractionation Coupled Proteomics ***Yunyang (Eileen) Zhou*** *(D4)*
Oral Presentation Session 2 *Chairs: Annie Roys, Rowan Pilkington*	LECTURE THEATRE 5
12.00 - 12.15 pm	Future burden of ischemic stroke in Australia: impact on health outcomes between 2019 and 2038 ***Tamrat Befekadu Abebe*** *(CMUS)*
12.15 - 12.30 pm	Structural Insights into the Activation of the Cholecystokinin Type 1 Receptor ***Jack Tovey*** *(DDB)*
12.30 - 12.45 pm	Can We Watch Drugs Bind? Elucidating Peptide Binding to NTS1 Receptor ***Herodion Adiwignyo Hartono*** *(MedChem)*
Lunch & Poster Viewing	COSSAR HALL
1.00 - 1.55 pm	**Lunch & Poster Viewing**
Poster Presentation Session 2: Group A (concurrent)	COSSAR HALL
1.10 - 1.15 pm	Tau-selective super-resolution fluorescent probes for deciphering Alzheimer's pathology ***Kaustubh Bhuskute*** *(MedChem)*
1.15 - 1.20 pm	Exploring the Relationship Between the LNP Formulation Components and Inflammatory Immune Response in mRNA-Vaccines ***Azizah Algarni*** *(D4)*
1.20 - 1.25 pm	Impact of nanoparticle size on lymph node biodistribution after subcutaneous injection in mice ***Muhammad Asim Farooq*** *(D4)*
1.25 - 1.30 pm	Contribution of intestinal ceramides to whole-body metabolic dysfunction ***Michael Mah*** *(DDB)*
1.30 - 1.35 pm	A lipid-based formulation facilitates lymphatic uptake of a protease inhibitor ***Yining Xie*** *(D4)*
1.35 - 1.40 pm	Exploring online teaching and learning in health professional education: a scoping review ***Lailaturrahmi*** *(PPSEd)*
1.40 - 1.45 pm	Developing new chemical tools to understand the biology of fatty acid binding protein 4 ***Imesha Lakmini Hettige*** *(MedChem)*
1.45 - 1.50 pm	Novel approaches to deliver betamethasone dipropionate for hand osteoarthritis treatment ***Hefeng Song*** *(D4)*
Poster Presentation Session 2: Group B *(concurrent)*	COSSAR HALL
1.10 - 1.15 pm	Marrying Activity with Permeability Towards Orally Bioavailable Somatostatin Peptide Therapeutics ***Travis Lay*** *(MedChem)*
1.15 - 1.20 pm	Delivery and expression of LNP mRNA in the secondary lymphoid organs drive robust immune responses ***Asuka Takanashi*** *(D4)*
1.20 - 1.25 pm	The impact of iron on fatty acid trafficking across the blood-brain barrier ***Showmika Tabassum Supti*** *(D4)*
1.25 - 1.30 pm	RAMP it up! Exploring conformational dynamics of the amylin 3 receptor (AMY3R) using HDX-MS ***Cameron Fairweather*** *(DDB)*
1.30 - 1.35 pm	New redox-active materials for manipulating cell signaling processes ***Katayoun Nazemi*** *(D4)*

1.35 - 1.40 pm	Teaching associates' perspectives of online teaching and learning in a pharmaceutical science degree ***Sarah Yang*** *(PPSEd)*
1.40 - 1.45 pm	Harnessing Solid Phase Synthesis in the Pursuit of Protein Degraders ***Liam Hales*** *(MedChem)*
1.45 - 1.50 pm	ShKT-Ts1, a novel peptide from the sea anemone Telmatactis stephensoni: Studies of the structure-function relationship in ShKT domain peptides ***Karol Sanches (MedChem)***
Oral Presentation Session 3 *Chairs: Eileen Zhou, Paulo Simon*	LECTURE THEATRE 5
2.00 - 2.15 pm	Revascularization and medication use following NSTEMI: analysis of 15,339 admissions in Victoria ***Adam Livori*** *(CMUS)*
2.15 - 2.30 pm	Fragment-based development of chemical probes for FABP4 ***Jason Pun*** *(MedChem)*
2.30 - 2.45 pm	Concept Inventory Development: A Comprehensive Systematic Review of Methodologies and Approaches ***Adeladlew Kassie Netere*** *(PPSEd)*
2.45 - 3.00 pm	Accelerating PROTAC discovery ***Jeyan Osman*** *(MedChem)*
Afternoon Tea & Closing Ceremony	COSSAR HALL
3.00 - 5.00 pm	**Afternoon Tea & Poster Viewing** **Symposium Closing & Award Ceremony**

PARKVILLE POSTGRADUATE ASSOCIATION

The **Parkville Postgraduate Association (PPA)** is the representative body for postgraduate students at Monash University Parkville Campus. PPA plays a diverse and multi-faceted role in academic, cultural and social aspects of student life. In addition to organising a multitude of social, academic and career events, PPA provides a means of representation for postgraduate students at the Parkville campus.

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EMCR Representative	Narges Mahdavian	DDB
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	Jess Huang	D4
	Katayoun Nazemi	D4
	Celine Hung	D4

PLENARY SPEAKER

Dr Craig Rayner

Curiosity and Empathy- An antidote to "Lost in Translation"?

Craig Rayner PharmD MBA FRCP Edin, is the Director of Regional Centre for Respiratory Medicine and Tropical Diseases at Moderna based in Melbourne, Australia. He is also an Adjunct Professor and Distinguished Alumnus of Monash University with >120 peer reviewed articles/chapters in clinical pharmacology, global health and infectious diseases. He has had leadership roles in the development and approval of several new medicines and oversight and peer advisory roles in many more. Throughout COVID pandemic, he lead prominent international R&D programs with Pharma, Biotech and NGOs and was a trusted advisor to governments and NGOs. Previously, he had senior global R&D roles in Switzerland, UK, USA and Australia, including at Roche and CSL, he was founding CEO of R&D advisory company d3 Medicine until its acquisition, and then President at Certara, leading it through a Nasdaq listing to US$7Bn market cap to become the key technology enabled R&D advisory firm, touching more than 90% of FDA approvals each year.

JUDGES

Thank you to the symposium judges for their time and contributions:

JUDGES Oral	THEME
Dr Dorothy Wai	Medicinal Chemistry
Dr Monica Langiu	Drug Discovery Biology
Dr Pouya Dehghankelishadi	Drug Delivery, Disposition and Dynamics
Dr Amanda Cross	Centre for Medicine Use and Safety
Poster	
Dr Sanja Bosnyak Gladovic	Drug Discovery Biology
Dr Sanju Babu Reddiar	Drug Delivery, Disposition and Dynamics
Dr Suzanne Caliph	Pharmacy and Pharmaceutical Sciences Education
Dr Kieran Stockton	Medicinal Chemistry
Dr Huong Nguyen	Drug Discovery Biology
Dr Parisa Badiee	Drug Delivery, Disposition and Dynamics
Dr Lauren Terry	Drug Discovery Biology
Dr Stephanie Newman	Drug Delivery, Disposition and Dynamics

AWARDS AND PRIZES

Thank you to the generous sponsors for providing the following prizes:

AWARDS	PRIZES	SPONSORS
Oral		
Most Outstanding Oral Presentation	$500	Chemist Warehouse
Second Place Oral Presentation	$300	BMG LABTECH
Third Place Oral Presentation	$150	AAPS
People's Choice Oral Presentation Award	$150	Lonza
Oral Presentation Encouragement Award	$100	Capella Science
Poster		
Most Outstanding Poster Presentation	$300	Formulytica
Second Place Poster Presentation	$200	Eppendorf
Third Place Poster Presentation	$150	Eppendorf
People's Choice Poster Presentation Award	$150	Enimera RegsPlus
Poster Presentation Encouragement Award	$100	Enimera RegsPlus

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Enimera RegsPlus is a consultancy business formed around the principles of health and wellness, innovation, and commercial success. With extensive experience across many therapeutic product types, Enimera RegsPlus offers Regulatory and related

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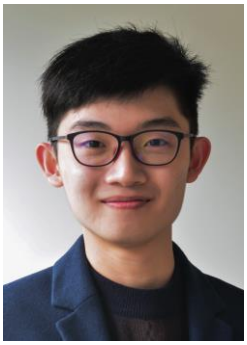
ABSTRACTS

Zijun Lu

Advanced materials to treat organ failure via inhibition of pancreatic enzymes in the gut

INTRODUCTION Acute and critical illnesses (ACIs) are typically managed in emergency and intensive care settings in hospitals. More than 20 million patients die per year worldwide from ACIs, predominantly due to progression to organ failure. Recently, the 'gut-lymph model' has demonstrated that 'toxic factors' from the gut enter the lymph and the blood circulation in ACIs, promoting systemic inflammation and organ dysfunction/failure. The major 'toxic factors' in the gut-lymph appear to be pancreatic lipases and proteases. Therefore, we investigated whether delivering small molecule inhibitors and/or adsorbent materials into the gut lumen could reduce pancreatic enzyme activity in the intestinal fluid and/or gut lymph, and its potential to reduce gut lymph toxicity. METHODS The in vitro loading and inhibition of pancreatic enzymes by different adsorbent materials, including mesoporous silica particles (MSPs) with different pore sizes (4-12nm), and activated charcoal, were tested. In vivo inhibition of pancreatic enzymes was assessed following infusion of adsorbent materials into isolated intestinal segments in rats. Finally, the efficacy of the adsorbent materials and small molecule enzyme inhibitors was tested in a rodent acute pancreatitis model. RESULTS AND DISCUSSION The adsorbent materials successfully adsorbed pancreatic enzymes (>50 mg/g) in a buffer medium. In addition, the results showed that MSPs and activated charcoal (more than 10 mg/mL) could significantly reduce trypsin and lipase concentrations in the rat intestine lumen (Figure 1). Finally, improvements in serum biomarkers of organ damage were achieved in the groups treated with pancreatic enzyme inhibitors. CONCLUSION Overall, this study found that adsorbent materials can inhibit pancreatic enzymes in the gut and gut lymph, and may provide a novel medical approach to reduce the progression of ACI to organ dysfunction and failure.

George Tan Shao Qian @_GeorgeTan



George Tan is a PhD candidate at the Centre for Medicine Use and Safety, under the mentorship of Dr. Jenni Ilomäki and Dr. Jed Morton. His research focuses on pharmacoepidemiology, specifically harnessing clinical big data to inform drug repurposing efforts. George's work focuses on generating new drug repurposing ideas and validating existing repurposing opportunities using administrative healthcare and patient registry data.

Effect of Different Resistance Mechanisms on Pseudomonas Aeruginosa Regrowth Against Meropenem

Traditional pharmacokinetic/pharmacodynamic (PK/PD) indices are based on minimum inhibitory concentrations (MICs) and link the response of bacterial pathogens with exposure to antibiotics. The PK/PD index most relevant for beta-lactam antibiotics is the time during which unbound antibiotic concentration exceeds the MIC (fT>MIC). We evaluated whether the effect of meropenem on isogenic bacterial strains of Pseudomonas aeruginosa with different resistance mechanisms is predicted solely by MIC or depends on the mechanism of resistance. Seven isogenic P. aeruginosa strains with upregulated efflux pumps (PAΔmexR), loss of entry porins (PAOD1), increased beta-lactamases (PAΔAD), a combination of two of these resistance mechanisms (PAΔDMxR, PAOD1MxR and PAOD1ΔD) and a wild-type reference strain (PAO1) were used. The meropenem MIC of each strain was determined. Then they were exposed to meropenem (1-64 mg/L) in static concentration time-kill studies (SCTK) over 72h. 1xMIC suppressed regrowth of PAOD1ΔD (16 mg/L) over 72h. 2xMIC suppressed regrowth of PAOD1 (8 mg/L), PAΔmexR (8 mg/L) and PAOD1MxR (32 mg/L). 4xMIC was required against PAO1 (4 mg/L), PAΔAD (8 mg/L), and PAΔDMxR (16 mg/L). Differences across strains were most marked in the 1-2xMIC range of the SCTK concentrations. The study indicated MIC alone did not predict the meropenem concentration required to suppress bacterial regrowth over 72h. At the same MIC, different resistance mechanisms might influence the meropenem concentration required to suppress regrowth. The study indicates traditional PK/PD indices do not fully explain the relationship between antibiotic exposure and bacterial response, and mechanisms of resistance may need to be considered when optimising atibiotic dosing.

Cheng (Selena) Peng

PhD Student (3rd Year) | DDB | Supervisors: Dr. Helena Qin, Dr. Elva Zhao, Dr. Elizabeth Vecchio, Professor Rebecca Ritchie, Professor Owen Woodman

Biased Agonism of Formyl Peptide Receptor 2 Governs Its signaling and trafficking profile

Background and Purpose There are increasing interests in developing FPR2 agonists (compound 43, ACT-389949 and BMS-986235), with ACT-389949 and BMS-986235 entered phase I clinical development as potential pro-resolving therapeutics. FPR2 activation leads to diverse downstream outputs; ACT-389949 is observed to cause rapid tachyphylaxis, while BMS-986235 and compound 43 induced cardioprotective effects in preclinical models. We aim to characterise the differences in ligand-receptor engagement and downstream signalling and trafficking bias profile. Experimental Approach Concentration-response curves to G protein dissociation, β-arrestin recruitment, receptor trafficking and second messenger signalling were generated using FPR2 ligands (BMS-986235, ACT-389949, compound 43 and WKYMVm), in HEK293A cells. Log(τ/KA) was obtained from the operational model for bias analysis using WKYMVm as a reference ligand. Key Results Bias analysis revealed that WKYMVm and ACT-389949 shared a very similar bias profile. In comparison BMS-986235 and compound 43 displayed approximately 5- to 50-fold bias away from β-arrestin recruitment and trafficking pathways, whilst being 35- to 60-fold biased towards cAMP inhibition and pERK1/2. Molecular docking predicted key amino acid interactions at the FPR2 shared between WKYMVm and ACT-389949, but not with BMS-986235 and compound 43. Conclusion and Implications In vitro characterisation demonstrated that WKYMVm and ACT-389949 differ from BMS-986235 and compound 43 in their signalling and trafficking profile. This observation may be explained by differences in the ligand-receptor interactions. In vitro characterisation provided significant insights into identifying the desired bias profile for FPR2-based pharmacotherapy.

Annie Roys

PhD Student (2nd Year) | D4 | Supervisors: A/Prof Darren Creek, Dr Carlo Giannangelo

Annie is a 2nd year PhD candidate in Creek lab. My research is focused on ways to reverse antimalarial resistance. I have served on PPA for 2 years and I have loved every moment of it. I am always keen for a chat and love to engage and network with new people, so if you see me around, definitely stop to say hi!

Targeting redox processes to treat drug-resistant malaria parasites

Resistance has been recorded for every class of antimalarial, including artemisinin combination therapies (ACTs), the current first line. Drug resistant parasites have been reported to have an increased ability to manage oxidative stress and maintain redox homeostasis following drug treatment, possibly due to an enhanced antioxidant system. We hypothesised that disrupting this redox balance by targeting the parasites' glutathione pathway will make parasites more susceptible to oxidative stress, and therefore re-sensitise them to existing antimalarials. This work aims to tackle resistance by identifying redox-modifying drugs that can be combined with artemisinin derivatives. Growth inhibitory studies and ring-stage survival assays were used to determine the antimalarial activity of different redox compounds and to identify compounds that could be synergistic with artemisinin *in vitro*. Real time analysis of parasite intracellular glutathione was observed using P. falciparum $NF54_{attB}^{[hGrx1\text{-}roGFP2]}$ parasite line and a plate reader based redox assay. Untargeted and targeted thiol metabolomic were carried out to identify metabolic changes in drug treated parasites. We identified sulforaphane (SFN) to be a promising candidate, which alters parasite redox status and potentiates the activity of artemisinin. The combination of 15μM SFN with 700 nM dihydroartemisin (DHA) in early ring-stage parasites resulted in a decrease in parasite survival compared to DHA alone (41% ± 7.3).15 μM SFN resulted in an increased oxidative burden within parasites after 1 h incubation. Untargeted and targeted thiol metabolomics confirmed that SFN's antimalarial activity is entirely redox mediated and not as a result of major metabolic changes within the parasite The addition of SFN to existing antimalarial therapies would re-sensitise resistant parasites to existing antimalarials thereby extending their life span. Ongoing studies will elucidate the mechanism responsible for this synergistic activity and determine the safety and efficacy of this approach in drug-resistant *in vivo* models of malaria.

Kai Kikuchi

PhD Student (2nd Year) | Med Chem | Supervisors: Dr Amandeep Kaur, Prof. Elizabeth J. New

Kai obtained his BSc in Chemistry and Medicinal Chemistry in 2018 at the University of Sydney. He then completed a GradDip and an MPhil in total synthesis of plant hormones under the supervision of Associate Professor Christopher S. P. McErlean. In 2021 Kai was awarded a scholarship to pursue PhD studies with Dr Amandeep Kaur, where his research is currently focused on the development of fluorescent tools to understand Alzheimer's disease. Outside of the lab, Kai can also be found experimenting in the kitchen with chemistry (cooking) or cell culture (fermenting and brewing).

Naphthalimides: A Novel Scaffold for Sensing the Micro-Environment of Amyloids

Amyloids are macromolecular aggregates that form when proteins assemble in a manner that generates a cross-β structure. Toxic amyloids are famously implicated in a wide range of diseases, most notably Alzheimer's and Parkinson's diseases, however less well known are functional amyloids that play important roles in normal biological functions. Despite two decades of research on functional amyloids, it remains unclear how cells can produce both toxic and functional amyloids under physiological conditions. To better improve our understanding of amyloids, it is important to understand the microenvironments (e.g., polarity, viscosity) presented on their surface, and how these affect their solubility and stability, and govern their interactions with lipid membranes and other hydrophobic surfaces in the cell. The challenges associated with studying amyloid are many. Structurally, amyloids and their pre-fibrillar oligomers can be heterogeneous in structure and size. In addition, traditional techniques such as fluorescence microscopy, electron microscopy, PET and SPECT do not give information about micro-environments. Fluorescence lifetimes are incredibly sensitive to the environment (e.g., polarity, viscosity) surrounding the fluorophore. Fluorescence lifetime microscopy (FLIM) can be used alongside environment-sensitive probes in order to gain information about differences in micro-environments within amyloid assemblies that cannot be visualised with other techniques In this presentation, I will discuss the design and testing of a library of naphthalimide-based fluorescent sensors that show both polarity and viscosity dependent fluorescence emission properties. I will also discuss their use in FLIM of amyloids, allowing us to distinguish different forms, as well as allowing mapping of micro-environments present within amyloid. We also extend this methodology to 3DFLIM, enabling 3-dimensional analysis of amyloid micro-environments.

Brigid McInerney

PhD Student (2nd Year) | CMUS | Supervisor: Prof Simon Bell, Dr Amanda Cross, Dr Justin Turner

Brigid is an accredited pharmacist with 10 years clinical experience in the care of older people in hospital and community settings. As Assistant Deputy Director of Pharmacy at Monash Health, she leads a team of pharmacy staff in the Rehabilitation and Geriatric Medicine program at Kingston Centre. Today, she's excited to share the findings of her PhD research to date, specifically a recent project to establish international consensus on the signs and symptoms of psychotropic adverse events that should be monitored in the nursing home setting.

Top 10 signs and symptoms of psychotropic adverse events to be monitored in nursing home residents

Introduction

International guidelines recommend monitoring for adverse drug events (ADEs) in people with dementia who are prescribed psychotropics such as antipsychotics, antidepressants and benzodiazepines. The aim of this study was to produce a consensus list of the top 10 signs and symptoms suggestive of psychotropic ADEs to be monitored in residents of nursing homes by nurses and care workers.

Methods

A systematic review resulted in a list of 41 signs and symptoms suggestive of psychotropic ADEs for possible monitoring. Through a 3-stage online Delphi survey, 51 participants from 13 Asia Pacific, European, and North American countries were invited to indicate their level of agreement with whether these signs and symptoms should be routinely monitored. Statements were included in the final list for prioritization if ≥70% of participants responded ≥7 on the 9-point Likert scale in Round 1 or ≥50% of participants responded ≥7 in Round 2, and excluded if ≤30% responded ≥7.

Results

Forty-four participants (93.6%) completed all 3 rounds. Participants included geriatricians, psychiatrists, general medical

practitioners, pharmacists, nurses and informal caregivers. Four of 41 signs and symptoms reached consensus for inclusion after Round 1, and 9 after Round 2. The top 10 signs and symptoms prioritized in Round 3 were: recent falls, daytime drowsiness or sleepiness, abnormal movements, confusion or disorientation, balance problems, dizziness, postural hypotension, reduced self-care, restlessness, dry mouth.
Conclusion
The consensus list of signs and symptoms for psychotropic ADE monitoring can be used to implement a proactive approach to identifying and addressing medication-related harm.

Muhammad Asim Farooq

PhD Student (2nd Year) | D4 | Supervisor: A/Prof Natalie L. Trevaskis

Asim is a 2nd year PhD student under the supervision of A/Prof Natalie Trevaskis and A/Prof Angus Johnston in the Drug Delivery, Disposition and Dynamics (D4) at Monash Institute of Pharmaceutical Sciences (MIPS), Monash University. His PhD project focuses on the interaction of nanoparticles with immune cells in lymph nodes. He received his master's degree in Pharmaceutics from China Pharmaceutical University Nanjing, China (2020) and received a Bachelor of Pharmacy (Doctor of Pharmacy) from the University of Sargodha, Sargodha, Pakistan (2017). He has published 10 papers as a first author and 28 papers as a co-author in peer-reviewed high-impact factor journals (Cumulative impact factor 200+).

Impact of nanoparticle size on lymph node biodistribution after subcutaneous injection in mice
Lymph nodes, which are rich in T cells, B cells, dendritic cells, and macrophages, are also primary sites of action for vaccines and immunotherapies. Promoting the delivery of immunotherapies and vaccines to lymph nodes has been found to enhance treatment efficacy.1,2 In this study, we investigated the particle effect of size on the lymph node uptake and biodistribution of negatively charged Cy5-polystyrene (PS) nanoparticles (NPs) (40 nm, 100 nm, and 250 nm) in mice following subcutaneous (SC) injection at 24 hr. The lymph node uptake and biodistribution were measured through in vivo imaging system (IVIS) and confocal microscopy. The concentration of Cy5 in the draining (ipsilateral) and non-draining (contralateral) lymph nodes (inguinal, popliteal, and iliac) is different after SC injection of the three different-sized NPs. The PS 40 nm particles led to significantly higher Cy5 concentration in inguinal draining (ipsilateral) LNs, inguinal non-draining (contralateral) LNs, and iliac contralateral LNs compared to the 100 nm and 250 nm particles at 24 hr. There was also a trend toward higher Cy5 concentrations in all LNs for the PS 40 nm compared to 100 and 250 nm particles. The concentration of all particles was higher on the dosing side than the non-dosing side, suggesting that they were taken up directly into the draining lymphatics. Overall, for all NPs, the concentrations of Cy5 across the lymph nodes were in the order inguinal > iliac > popliteal, which is expected based on lymphatic drainage patterns from the leg side. Consistent with the LN biodistribution data, confocal microscopy images also indicated that Cy5 signals of 40 nm PS NPs were higher in the draining inguinal lymph compared to 100 and 250 nm PS NPs. This work demonstrates the important effect of NP size on lymph node uptake and distribution to immune cells in lymph nodes where the smaller 40 nm NPs were found to yield higher delivery to the LN immune cells. This has important implications for the optimal design of NPs for vaccines and immunotherapies.

Isabella C Russell

PhD Student (3rd Year) | MedChem | Supervisor: Prof Patrick Sexton, Prof Denise Wootten, Dr Xin Zhang, Dr Matthew Belousoff

Development of Small Lipid-dependent activation of the orphan G protein-coupled receptor, GPR3
Over 800 G protein-coupled receptors (GPCRs) are encoded for by the human genome, with the importance of these receptors highlighted by their role as drug targets, where GPCRs comprise ~30% of currently marketed drugs. Despite the considerable interest in GPCRs, the endogenous ligands for around 100 receptors remain unknown; these receptors are termed orphan GPCRs (oGPCRs). GPCRs canonically bind to a G protein heterotrimer (comprising of α, β and γ subunits) to initiate intracellular responses. Whilst agonist binding is traditionally required for G protein association and activation, some GPCRs can productively engage G proteins independent of ligand. GPR3 is a class A oGPCR, expressed in the central nervous system and adipose tissues. Although tool compounds and potential ligands for the receptor have been proposed, no endogenous ligands have been validated. Recent data suggests that the physiological activity of GPR3 might be primarily driven by constitutive signaling, with regulation of GPR3 responses achieved through changes to receptor expression. This work presents the novel structure of GPR3, in complex with DNGαs and Gβ1γ2 subunits, revealing that GPR3 is a lipid activated receptor, with the previously described constitutive activity of the receptor likely due to high occupancy of the receptor by an endogenous lipid(s). Additionally, 3D variability analysis of the dynamics of the active complex provided potential mechanistic insight into entry/egress of the lipid that may be linked to receptor

activation. This work provides key information for understanding of the biology of GPR3 and extends our knowledge of GPCR activation mechanisms.

Jackson He

PhD Student (3rd Year) | MedChem | Supervisors: Prof Philip Thompson, Prof Jake Shortt

Completing a Bachelor of Pharmaceutical Science (Advanced Honours) in 2020, Jackson chose to pursue a PhD in the Medicinal Chemistry theme. Under the supervision of Prof Philip Thompson and Prof Jake Shortt, he has a keen interest in the development and transition of promising therapeutic compounds from the chemistry laboratory to biological systems. His current work investigates suitability of multitarget inhibitors as a strategy for future cancer therapy, with the goal of discovering safer and more targeted treatments for T-cell lymphomas.

Dual BET and PI3K inhibitors for the treatment of T-cell non-Hodgkin Lymphoma

T-cell lymphomas (TCL) are a rare group of non-Hodgkin lymphoma (NHL) that are often associated with poor responses and dismal prognosis. Chemotherapy regimens such as cyclophosphamide, doxorubicin, vincristine and prednisolone are often favoured as first-line treatments, however are often associated with poor outcomes and resistance acquisition. Thus, the complexity and rarity of both these disease groups in addition to ineffective first-line treatments have highlighted the need for novel TCL specific therapies. Recent clinical trials and pre-clinical work have shown the importance of phosphatidylinositol kinase (PI3K) blockade in cutaneous and peripheral T-cell lymphoma, with further clinical trials demonstrating increased synergistic efficacy when coupled with histone deacetylase inhibitors. In this study, we describe our pre-clinical investigation into combination treatments of dual PI3K and bromodomain and extra-terminal (BET)-bromodomain inhibition across a series of TCL cell lines. Key techniques employed for this study involves the use of competitive binding and enzyme assays in parallel with cell biology techniques to investigate the therapeutic potential of PI3K and BET inhibition in TCL. Our findings present a unique look into the cooperation between PI3K and BET inhibition by 18DS as a strategy for the treatment of cutaneous and peripheral T-cell lymphoma.

Amelia Miklavec

PhD Student (2nd Year) | D4 | Supervisors: A/Prof Joseph Nicolazzo, Dr Liam Koehn

I am a second year PhD student at Monash University in the Drug Delivery, Disposition, and Dynamics theme under the supervision of Associate Professor Joseph Nicolazzo. My project focuses on fatty acid binding proteins and their role in inflammation, particularly in the context of motor neurone disease. Apart from my PhD, I am also a casual teaching associate, hospital pharmacist, and marketing assistant for Her Research Matters. I am also very passionate about student welfare at Parkville, and particularly enjoy my role as Vice-President and Social Officer for the Parkville Postgraduate Association. I look forward to meeting you all.

Modulation of microglial fatty acid binding protein 4 to reduce neuroinflammation in MND.

Excessive inflammation negatively impacts many neurodegenerative disorders, including amyotrophic lateral sclerosis (ALS). In ALS, microglia are activated, causing prolonged inflammation that damages surrounding neurones and induces cell death. Activated microglia have upregulated fatty acid binding protein 4 (FABP4), that may contribute to neurodegeneration by upregulating the inflammatory response. FABP4 inhibition can decrease the microglial inflammatory response, and therefore may slow neurodegeneration. However, the extent of FABP4 expression and impact of FABP4 inhibition in the context of ALS, which has pronounced neuroinflammation, is unknown. Therefore, this study aims to identify the abundance of FABP4 expression in microglia from an ALS mouse model, and in human microglia derived from induced pluripotent stem cells from healthy and ALS patients. The impact of chemical FABP4 inhibition will also be assessed, alongside concentration of the inhibitor in the brain and spinal cord in addition to the ratio of penetration. Currently, BMS309403 is the most commonly studied FABP4 inhibitor due to its high potency and selectivity. However, it is highly lipophilic, making delivery to aqueous systems difficult. To resolve this, novel FABP4 inhibitors have been designed using fragment-based drug discovery. If in vitro studies show decreased inflammation following FABP4 inhibition, SOD1G93A mice will be treated with or without a penetrable inhibitor to assess neuroinflammation. Western blot and enzyme-linked immunosorbent assay quantification will determine inflammatory mediator expression, such as interleukin-6 and tumor necrosis factor alpha. Determining the impact of FABP4 inhibition may open an avenue for novel ALS treatments to slow the progression of this debilitating disease.

Eric Toan Le Tran

PhD Student (4th Year) | MedChem | Supervisors: Dr. Manuela Jörg, Dr. Amandeep Kaur, Dr. Yi Sing Gee

Eric completed his Bachelor of Pharmaceutical Science and Honours degree, majoring in Medicinal Chemistry at Monash University in 2017. His research project was with Professor Jonathan Baell, where he explored the structure activity relationship of P2Y14 receptor antagonists. He is currently undertaking his PhD under the supervision Dr Manuela Jörg, Dr Amandeep Kaur and Dr Yi Sing Gee at the Monash Institute of Pharmaceutical Sciences. His research focuses on exploring the utility of reduction-activated moieties as probes, prodrugs and anti-tuberculosis agents.

EXPLORATION OF PHENOXAZINE DERIVATIVES FOR THE TREATMENT OF TUBERCULOSIS

Tuberculosis (TB) is currently the second leading cause of death by an infectious disease, only behind COVID-19. The World Health Organisation (WHO) reported a total of 1.6 million people succumbing to the disease, with an estimated 10.6 million people falling ill with TB worldwide in 2021.1 The causative agent behind this disease is Mycobacterium tuberculosis (Mtb) and can be fatal if left untreated. While treatments are available for this disease, the emergence of resistant strains to first-line and second-line treatment options make this disease an ongoing public health concern.2 Therefore, the development of new treatment regimens, repurposing of existing drugs as well as the discovery for new drugs are necessary to combat the disease.3

Herein, we report our efforts to explore the structure-activity relationship (SAR) of a phenoxazine-derivative, which was identified as a hit with sub-micromolar activity against a Mtb strain through a phenotypic compound screen. The hit had no antibacterial activity when tested against S. aureus, E. faecium, E. coli, K. pneumoniae, A. baumannii and P. aeruginosa. Modifications to different parts of the structure have thus far revealed “steep” SAR. Interestingly, the activity of the hit compound was completely abolished against a mutant strain of TB, while the other analogues retained activity against the resistant Mtb strain.

William Parsons

PhD Student (3rd Year) | MedChem | Supervisors: Dr. David Chalmers, Prof. Phil Thompson

Will Parsons completed his Bachelors of Pharmaceutical Sciences with Advanced Honours in 2020. He has since continued his research journey with a PhD in the theme of Medicinal Chemistry under the supervision of Dr. David Chalmers and Prof. Philip Thompson. His interests include de novo design of synthetic proteins, synthetic methodologies and structural characterisation of biologically relevant materials. His current project is focused on the development of biomimetic ion channels as potential chemical biological tools.

Design and Synthesis of Covalently Tethered Asymmetric Tetrameric Cyclic Peptide Nanotubes

Peptide nanotubes formed through secondary and tertiary structures are an emerging area of chemical biology. Head-to-tail cyclised peptides with alternating D/L-amino acids form nanotubes through a well-ordered hydrogen bonding network. Cyclic peptide nanotubes (CPNs) based on these materials are able to form long networks of nanotubes that demonstrate applications in a number of areas such as drug delivery systems, biomimetic membrane channels and bioorganic electronic devices. CPNs generated from self-assembled monomers have limited control over the assembly mechanism and consequently the supramolecular structure. This can be overcome by covalently tethering monomeric cyclic peptides to improve control over the self-assembly. Symmetrical tethers have shown to be an effective tethering strategy, however, it limits the ability to selectively functionalise CPNs.

By introducing asymmetrical tethering strategies, we can develop more specific structures tailored for more specific applications. This work looks to design and synthesise asymmetric CPNs that are able to embed within membranes. Several covalently tethered asymmetric tetramer designs were computationally modelled to evaluate their stability in a membrane environment. The desirable tetramer designs were attempted to be synthesised using a variety of orthogonal protecting groups and tethering strategies.

Pooja Maharjan

PhD Student (2nd Year) | D4 | Supervisors: Prof Michelle McIntosh, Prof Joshua P Vogel, Dr Annie McDougall, and Mr. Pete Lambert

Pooja Maharjan completed her Bachelor of Medical Laboratory Technology from Nepal and a trained Laboratory Technologist. She went to South Korea for continuing her career in academic and research where she completed her master's degree in pharmacy majoring in biopharmaceutical sciences. While doing her master's degree, she worked as research assistant in the lab of biopharmaceutical sciences and continued her job after the degree as well for half a year. Currently, she is a PhD candidate in Drug Delivery, Disposition and Dynamics (D4) at Monash Institute of Pharmaceutical Sciences. Her project is focused on global health where she is working on evaluating the quality of maternal medicines from few low- and middle-income countries.

Quality of medicines for the management of hypertensive disorders of pregnancy: a systematic review

In 2020, globally, an estimated 287,000 women died due to complications of pregnancy and childbirth, equating to 223 maternal deaths per 100,000 live births. Hypertensive disorders of pregnancy are the second-leading cause of maternal mortality, accounting for approximately 27,830 deaths in 2019. Medicines such as magnesium sulphate, aspirin, calcium supplements, and antihypertensives-nifedipine, methyldopa, hydralazine, labetalol, amlodipine and enalapril, are recommended for the prevention, and treatment of hypertensive disorders of pregnancy. It is critical to access to quality medicines. There is evidence that the quality of medicines for pregnancy-related conditions is substandard in many low- and middle-income countries. Ineffective medicines thus present a major challenge to reaching the Sustainable Development Goal of reducing the global maternal mortality ratio to 70 deaths per 100,000 livebirths by 2030. Although several studies have been carried out assessing the quality of magnesium sulphate, aspirin, calcium supplements and antihypertensive medicines, the evidence from these studies has not been systematically synthesized.

Adam Livori @cardiopharmnerd

PhD Student (2nd Year) | CMUS | Supervisors: Prof Simon Bell, Prof Zanfina Ademi, Dr Jedidiah Morton

Adam Livori is a cardiac clinician researcher currently completing his PhD in pharmacoepidemiology, health economics and translational science. He works clinically as consultant cardiology pharmacist at Grampians Health, overseeing medical specialties and ambulatory care in cardiology. His research interest includes applied biostatistics and health economic analysis. His passionate about open-source science and currently holds research funding under Safer Care Victoria, and collaborates between CMUS and the Victorian Heart Institute. His PhD title is "Patterns and predictors of clinical outcomes in myocardial infarction and atrial fibrillation.

Is remoteness associated with secondary prevention medications post STEMI?

Aim

Background:

People in rural and remote areas may have poorer cardiovascular outcomes than people in metropolitan areas. The objective of this study was to analyse differences in receiving and adhering to secondary prevention medications following ST elevation myocardial infarction (STEMI) by remoteness in Victoria.

Method:

All individuals discharged between 1 July 2012 and 30 June 2017 and alive at 90 days post-discharge were identified through the Victorian Admitted Episodes Dataset (n=12,015). Receipt (within 90 days) and 12-month adherence (defined as ≥80% proportion of days covered) to beta-blockers (BB), ACE inhibitors or angiotensin receptor blockers (ACEI/ARB), P2Y12 inhibitors (P2Y12i) and statins were estimated via linkage to the Pharmaceutical Benefits Scheme. Remoteness was quantified using the Accessibility/Remoteness Index of Australia (ARIA). Adjusted odds ratios (OR) and 95% confidence intervals (CIs) for receipt and adherence were estimated using logistic regression.

Results:

Following STEMI, 69% of people received BB, 77% ACEI/ARB, 75% P2Y12i and 80% statins. For each one-unit increase in ARIA score, ORs were 0.98 [95%CI 0.92-1.03] for receipt of BB, 1.00 [95%CI 0.94-1.08] for ACEI/ARB, 0.91 [95%CI 0.83-0.98] for P2Y12i and 1.06 [95%CI 0.96-1.18] for statins. For each one-unit increase in ARIA score, ORs for 12-month adherence were 1.04 [95%CI

0.98-1.10] for BB, 1.15 [95%CI 1.09-1.22] for ACEI/ARB, 1.16 [95%CI 1.09-1.24] for P2Y12i, and 1.14 [95%CI 1.08-1.21] for statins.
Conclusion:
Remoteness does not appear to affect initial dispensing of secondary prevention medications within 90 days post-STEMI. Remoteness is not a driver of non-adherence if patients are dispensed initial secondary prevention therapy.

Annie Luo @AnnieP_Luo

PhD Student (4th Year) | D4 | Supervisors: A/Prof Darren Creek, Dr Ghizal Siddiqui

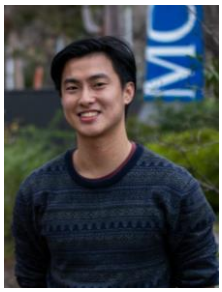
I am a final year PhD student from the Creek Lab in D4. My project is to investigate the mode of action of a novel antimalarial candidate using untargeted drug target identification proteomics and targeted functional bioassays. My vision is to combine system biology and novel biotechnology to empower and advance current research in global therapeutic areas.

Potent and irresistible bis-1,2,4-triazines likely target the parasite nucleus

Bis-1,2,4-triazines are a class of fast-acting antimalarial candidates with low-nanomolar potency against asexual and early sexual blood stage Plasmodium falciparum. Whilst their peak activities are observed against the trophozoites, the lead bis-1,2,4-triazine can kill rings within 5 hours with IC50 below 100 nM. Their mode of action is elusive to date, however, appears to be novel, as no cross-resistance has been observed to a wide range of drug-resistant parasites. In order to investigate their mode of action, we have attempted to select for bis-1,2,4-triazine-resistant parasites in vitro. No resistance could be generated in the hypermutable Dd2-Polδ parasites or subjecting a step-wise drug challenge to Pf3D7 and PfDd2 over 24 months. This indicates that bis-1,2,4-triazines have a very low propensity for resistance emergence. We also employed complementary untargeted proteomics methods to identify the potential target(s) of bis-1,2,4-triazines, one of which is live cell thermal stability proteomics. When we applied this method to representative bis-1,2,4-triazines, and the lead compounds stabilised 21 nuclear proteins at 65°C with a fold-change >1.5 ($p < 0.05$). Some of these proteins play important roles in DNA repair, DNA replication and gene expression. In order to validate these results, we are currently performing an orthogonal chemoproteomic approach, limited proteolysis-MS, to more precisely identify which of these represent the primary target of bis-1,2,4-triazines.

Scott Wong

PhD Student (3rd Year) | MedChem | Supervisors: A/Prof Ben Capuano, A/Prof Karen Gregory, Prof Peter Scammells



Scott Wong holds a Bachelor of Pharmaceutical Science (Honours) degree from Monash University in Melbourne, Australia since 2020. Under the supervision of Associate Professor Ben Capuano and Professor Peter Scammells, Scott's Honours project focused on the design and synthesis of MAP4K4 inhibitors for the treatment of Amyotrophic Lateral Sclerosis (ALS). With continual interest and bursarship from the Cyril Tonkin Scholarship, Scott is able to pursue research into neurodegenerative diseases across the Capuano, Scammells and Gregory groups at the Monash Institute of Pharmaceutical Science (MIPS). His PhD candidature combines Chemical Biology techniques to design, synthesise and biologically evaluate biased allosteric modulators of the Metabotropic Glutamate Receptor Subtype 5 (mGlu5); a protein receptor known to be implicated in a wider range of neurodegenerative diseases (e.g. Alzheimer's, Parkinson's, ALS, etc.).

Developing Allosteric Ligands of the Metabotropic Glutamate Receptor Subtype 5 as CNS therapeutics

Glutamate is a crucial neurotransmitter responsible for key brain functions, such as memory and learning. Disruption and imbalances within the glutamatergic signalling pathway can often lead to a variety of central nervous system (CNS) diseases. However, CNS diseases are often treated with symptomatic therapeutics and do not address the disease state itself or produce undesired side effects. The metabotropic glutamate receptor subtype 5 (mGlu5) is a class C GPCR indicated within a variety of central nervous system (CNS) diseases. As part of the glutamatergic system, the mGlu5 is a clinical target for the regulation and homeostasis of many CNS diseases. Currently, allosteric modulators of the mGlu5, such as BMS-984923, have begun a new era of finely-tuned drugs for CNS disorders. Allosteric ligands stabilize mGlu5 in various unique conformations that could bring forth biased signalling towards therapeutic effects and avoid adverse effects. Recent noteworthy studies have linked desirable effects found in in vivo profiles to an in vitro signature, easing the design of future mGlu5 allosteric modulators at a very early stage of drug discovery. Subsequently, positive allosteric modulators (PAMs), negative allosteric modulators (NAMs) and neutral allosteric ligands (NALs) of mGlu5 are all of interest as tentative therapeutics for a myriad of CNS disorders.
Here we report a design, synthesis and biological evaluation of novel allosteric ligands of the mGlu5. We employ key biochemistry techniques to create novel allosteric ligands with the ability to engender bias signalling towards therapeutic effects and avoid adverse effects.

Zahra Abousalman Rezvani

PhD Student (3rd Year) | D4 | Supervisors: Prof. Nicolas H. Voelcker

Zahra Abousalman-Rezvani has received her bachelor's degree in polymer engineering in 2016. Her master studies on drug delivery systems were carried at Sahand University of Technology in Tabriz, Iran. Afterward, she is proceeding with her scientific career as a Ph.D. candidate with the focus on synthesis stimuli-responsive polymers via reversible addition-fragmentation chain transfer polymerization at Monash University and the commonwealth scientific and industrial research organization. Her present research interests involve the self-assembly of block copolymers, stimulus-responsive co-polymers as well as their potential applications on gene delivery systems.

siRNA Delivery using Polymer-Grafted Porous Silicon Nanoparticles

RNA interference induced by small interfering RNA (siRNA) is a promising strategy for the treatment of various diseases including cancer. However, a diverse set of challenges (e.g., rapid enzymatic digestion, poor cellular uptake, and lysosomal degradation) hamper the clinical application of siRNA. Therefore, it is necessary to develop innovative delivery strategies to overcome these limitations and enhance siRNA's therapeutic potential in cancer treatment. The aim of this study is to customize porous silicon nanoparticles (pSiNPs) for siRNA delivery through (co)polymer grafting. The high surface area of the pSiNPs provides the opportunity to achieve high engraftment of (co)polymer in both surface and pores. This polymer coating is finetuned for enhancement of siRNA loading, protection and cellular uptake/ transfection.

The co(polymer) coating was fully physiochemically characterized and afterwards, PDMAEMA and POEGMA-b-PDMAEMA coated pSiNPs were compared head-to-head in terms of siRNA loading, protection and cellular association. Polo-like kinase (PLK1) siRNA was used as a well-established siRNA payload with anti-cancer properties to further compare these two formulations in terms of silencing efficacy and the effect on metabolic activity and apoptosis rate in MDA-MB 231 and MDA-MB 468 breast cancer cell lines.

Both siRNA-pSiNP nanoformulations showed protection against RNase treatment. PDMAEMA coated NPs had a slightly higher cellular association. Both nanoparticles loaded with PLK1-siRNA showed a significant reduction of metabolic activity of MDA-MB 231 and MDA-MB 468 cells compared to non-targeting control (NTC) siRNA loaded particles.

Marisa Geovanna Santibanez Moran

PhD Student (2nd Year) | MedChem | Supervisors: Dr Manuela Jörg, Prof. Philip Thompson & Dr Chiara Maniaci

FLUORESCENT PROTEIN DEGRADERS FOR BROMODOMAIN-CONTAINING PROTEIN 4

Chemical probes play a key role in providing critical information to understand the role of proteins in health and disease by evaluating the level of expression, functional activity and localization of proteins. To be able to provide this information accurately, probes need to be sufficiently potent and highly selective for their target protein, which makes their design challenging. PROTACs are heterobifunctional molecules that induce the degradation of a target protein by the ubiquitin-proteasome pathway. Their unique mode of action provides some advantages for the development of chemical probes compared to traditional small molecules. In the present work, we aimed to develop a new class of chemical probes by combining fluorescence technology with targeted protein degradation. By combining the visualisation capabilities of fluorescent probes with the advantages of PROTACs, we will be able to understand more about how PROTACs work on a molecular level. Here, we designed and synthesised the first series of trivalent fluorescent PROTACs for bromodomain-containing protein 4 (BRD4). We installed a fluorescein fluorophore into a previously reported BRD4 trivalent PROTAC (1,2,5T-EG2-MZ1). We synthesised a set of six BRD4 trivalent fluorescent PROTACs (TFPs) with varying linker lengths. Preliminary results showed that the trivalent fluorescent PROTACs retain similar fluorescent intensity to fluorescein alone, as well as modest degradation of BRD4 induced by probes TFP1, TFP2, and TFP6.

Tamrat Befekadu Abebe @tamrat_ab2012

PhD Student (2nd Year) | CMUS | Supervisors: Professor Zanfina Ademi

Tamrat Befekadu Abebe is a second-year doctoral student at Centre for Medicine Use and Safety in Monash University. His project focused on understanding the current and future burden of cardiovascular disease from health and economic perspective and building a state-of-the-art economic evaluation models for comparing cardiovascular disease treatments. He holds a Master's in health economics from Karolinska institutet, Sweden, and a Bachelor of Pharmacy from University of Gondar, Ethiopia. He has experience in working in academia and industry. His aspiration is to enhance people's well-being by influencing policies concerning cardiovascular disease based on the best available evidence.

Future burden of ischemic stroke in Australia: impact on health outcomes between 2019 and 2038

Background: Projections of the future burden of ischemic stroke (IS) has not been extensively reported for the Australian population; the availability of such data would assist in health policy planning, clinical guideline updates, and public health.
Methods: Multistate lifetable model was constructed to estimate the lifetime risk of IS and to project the health burden of IS over a twenty-years period (2019-2038) for Australian people aged between 40 and 100 years. The Victorian linked dataset was primarily used to source data for the model.
Results: The lifetime risk of IS from age 40 years was 15.5% for males and 14.0% for females in 2018. From 2019-2038, 644 208 Australians were projected to develop incident IS (564 922 non-fatal and 79 287 fatal). By 2038, the model projected there would be 358 534 people with prevalent IS, and in 2038 there would be 35 554 incident of non-fatal IS and 5 338 incident of fatal-IS, a 14.2% (44 535), 72.9% (14 988) and 106.3% (2 751) increase compared to 2019 estimations, respectively. Projected years of life lived (YLL) (5% discount) accrued by the Australian population were 174 782 672 (84 251 360 in males and 90 531 312 in females), with 4 053 794 YLL among people with IS (2 320 513 in males, 1 733 281 in females).
Conclusion: The burden of IS was projected to increase between 2019 to 2038 in Australia. The outcomes of the model provide important information for decision-makers to design strategies to reduce stroke burden.

Jack Tovey

PhD Student (3rd Year) | DDB | Supervisors: Prof. Patrick Sexton; Prof. Denise Wootten; Dr. Matthew Belousoff; Dr Jesse Mobbs; Dr Brian Cary

Tamrat Befekadu Abebe is a second-year doctoral student at Centre for Medicine Use and Safety in Monash University. His project focused on understanding the current and future burden of cardiovascular disease from health and economic perspective and building a state-of-the-art economic evaluation models for comparing cardiovascular disease treatments. He holds a Master's in health economics from Karolinska institutet, Sweden, and a Bachelor of Pharmacy from University of Gondar, Ethiopia. He has experience in working in academia and industry. His aspiration is to enhance people's well-being by influencing policies concerning cardiovascular disease based on the best available evidence.

Structural Insights into the Activation of the Cholecystokinin Type 1 Receptor

Obesity is an ever-growing health burden, occurring when nutritional homeostasis is perturbed by consistent caloric surplus. The process of caloric assimilation is governed in part by the activity of the neuroendocrine peptide cholecystokinin (CCK). CCK influences function in a range of gastrointestinal tissues and the associated peripheral nervous system (PNS). CCK has attracted attention from pharmaceutical companies for its activity in the PNS; where CCK activation of the Cholecystokinin Type 1 Receptor (CCK1R) suppresses appetite. CCK1R accomplishes its function via activation of Gαq signalling, which has been a model small molecule agonist drugs. Several such drugs have progressed to clinical trial since 2000, but no candidate has proven superior to a calorie restricted diet.
This project uses single particle cryo-EM to determine the structure of CCK1R in complex with small molecules agonists: SR146131 (SR1), GI181771X (GIX), and Compound1 (CD1). SR1 and GIX are potent agonists of the CCK1R-Gαq pathway, that were discontinued after clinical trial failures. Both molecules have conflicting literature suggesting both allosteric and orthosteric mechanisms. CD1 was first identified as an allosteric intervention with limited agonism for the CCK1R-Gαq pathway.
CCK1R-Gαq complexes with each ligand have been purified. The first novel structure: SR1-CCK1R-Gαq was modelled at 3.2Å, showing SR1 bound orthosterically. Grid conditions are being optimized for GIX-CCK1R-Gαq and CD1-CCK1R-Gαq data collection.

Comparison of the binding positions of each of these molecules can supplement the existing CCK1R model of agonism. These results may in time contribute to the development of new therapeutics for the treatment of obesity.

Herodion Adiwignyo Hartono

PhD Student (3rd Year) | MedChem | Supervisors: Dr David K. Chalmers and A/Prof Daniel J Scott

Can We Watch Drugs Bind? Elucidating Peptide Binding to NTS1 Receptor.
Structures of ligand protein complex obtained from X-ray crystallography or cryo-EM often lack the information regarding intermediate stages of the binding-unbinding pathway between solution phase to the final binding pose. Understanding the binding-unbinding pathway is key to understanding ligand selectivity for specific subtypes, a feature needed for the next generation of GPCR drugs. Molecular dynamics simulations could bridge this gap. However, current conventional molecular dynamics simulations have very short timescales compared to binding and unbinding events. The timescale gap made it difficult to observe the dynamic pathway between solution phase and bound ligand, therefore the application of such methods are computationally very expensive. Other methods that use biased energy such as metadynamics often unrealistic conformations that prevents the trajectories to be used as SBDD visual aid.
We employed parallel cascade selection molecular dynamics to elucidate the binding pathway of neurotensin 1 receptor peptide ligand without the use of biased energy methods. We demonstrated the replication of bound ligand conformation in published structures of the neurotensin 1 receptor from solution phase ligand.

Yunyang (Eileen) Zhou linkedin.com/in/yunyang-zhou-248666198

PhD Student (2nd Year) | D4 | Supervisors: A/Prof Darren Creek, Dr Ghizal Siddiqui

Yunyang (Eileen) Zhou is a passionate PhD student delving into the complexities of malaria research. Her focus centers on investigating the mechanisms of action of a novel antimalarial compound through multiomics approaches. She actively participates in domestic conferences, presenting her research and gaining valuable exposure. Committed to advancing our understanding of malaria, Eileen aspires to contribute to the development of more effective antimalarial strategies for global health.

Exploring PfExportin-1 as a Novel Antimalarial Target via Nuclear Fractionation Coupled Proteomics
The rapid emergence of artemisinin resistance highlights the urgent imperative for new antimalarials. A novel drug class 2-aminobenzimidazoles (ABIs) have exhibited remarkable potency against the erythrocytic stage of Plasmodium falciparum. Preliminary studies have identified P. falciparum exportin-1 (PfXPO1), involved in nucleocytoplasmic export, as a potential ABI target. Notably, an ABI-resistant strain R1 revealed a H1061N point mutation within PfXPO1. To validate PfXPO1 as an ABI target, we developed a nuclear fractionation-coupled proteomics approach, probing nucleocytoplasmic transport between trophozoite stage parasites of the ABI-resistant line R1 and parent line DD2.
Analysis of nuclear fractions identified 85 significantly different proteins between R1 and the parent line DD2, whereas 69 proteins showed significant disparity in cytosolic fractions. Gene ontology analysis revealed perturbed proteins involved in DNA transcription, gene expression process, cellular oxidant detoxification and localization to cellular compartments such as RNA polymerase II. Notably, some perturbed proteins contained nuclear export signal (NES) binding regions for export through PfXPO1.
These findings support the role of PfXPO1 in nucleocytoplasmic transport of transcription-associated proteins. Further investigations aim to elucidate the mechanism of ABI resistance induced by H1061N mutation, by comparing nuclear and cytoplasmic proteome changes in R1 and DD2 parasite lines upon ABI treatment.

Kaustubh Bhuskute

PhD Student (2nd Year) | MedChem | Supervisors: Dr Amandeep Kaur

Kaustubh completed bachelor's program in Pharmacy in 2019 at the University of Mumbai. He then received a rare Danish Government scholarship to pursue the master's degree program in Medicinal Chemistry at the University of Copenhagen which he completed in 2021. His master's thesis focused on the design and synthesis of agonists for the G protein-coupled receptor GPR183 under the supervision of Professor Trond Ulven. In 2022, he received a scholarship to undertake PhD studies with Dr Amandeep Kaur. His research focuses on the development of fluorescent tools for super-resolution imaging of amyloids. In his spare time, Kaustubh enjoys reading science fiction, playing table tennis, and is a cricket enthusiast.

Tau-selective super-resolution fluorescent probes for deciphering Alzheimer's pathology

Dementia affects 55 million people across the world and is the second leading cause of death in Australia. Alzheimer's disease (AD) is the most common form of dementia. Amyloids play a critical role in the development of AD but there is still a lack of clear understanding of pathology of this disease. A robust correlation has been established between the load of tau amyloid aggregates resulting from tau proteins and the progression of AD which makes it a biomarker of importance for studying the complexities of AD. However, tau amyloids have not yet been explored as thoroughly as Aβ, the other biomarker of AD. Understanding the role and stages of tau assemblies in AD pathology requires studying them at the molecular scale. While super-resolution imaging can afford imaging at the nanoscale, to our knowledge there are no super-resolution fluorescent probes selective for tau.

We here synthesize a library of super-resolution fluorescent probes selective for tau amyloids. These probes comprise a tau-binding moiety which is linked to a photoswitching fluorophore via linkers of variable length. From the binding affinity data, we demonstrate the several-fold selectivity of these probes for tau amyloids over Aβ. We also explore the impact of linker lengths on the binding affinity and fluorescence properties of these probes. Ultimately, we use a super-resolution imaging technique- dSTORM, to elucidate the morphology of tau assemblies, thus shedding more light on tau pathology and helping decode the unsolved puzzle of AD.

Azizah Algarni

PhD Student (2nd Year) | D4 | Supervisors: Dr. Angus Johnston and Prof. Colin Pouton

Azizah Algarni is a dedicated second-year PhD student at Monash University's Faculty of Pharmacy and Pharmaceutical Science. Under the expert guidance of Professors Colin Pouton and Angus Johnston, Azizah is passionately involved in an mRNA delivery development project. Her PhD research is dedicated to unravelling the source and mechanism of the adjuvant activity in lipid nanoparticles used for the COVID-19 mRNA vaccine, which is a very important aspect in improving the safety and efficacy of lipid nanoparticle formulations for future mRNA vaccines.

Her academic journey commenced with a Bachelor's degree in Clinical Pharmacy from Umm Al-Qura University in Saudi Arabia in 2015. Azizah's commitment to scientific research led her to complete her Master's degree in 2021 at Monash University, during which she gained valuable skills in in-vivo and ex-vivo techniques for evaluating lipid nanoparticle efficiency and distribution. She has also made significant contributions to her field with three publications in peer-reviewed journals since 2020. Azizah's dedication to pharmaceutical science promises to drive innovation and progress in mRNA vaccine technology.

The influence of ionizable cationic lipids on organ-selective gene expression

In vivo delivery of plasmid DNA by lipid nanoparticles: the influence of ionizable cationic lipids on organ-selective gene expression.

Tracey Luu

PhD Student (2nd Year) | MedChem | Supervisors: Dr. Manuela Jörg

Tracey Luu completed her Bachelor of Science degree in Chemistry at the University of Melbourne in 2017. Her research project was with Dr. Yuning Hong on the development of cysteine-reactive fluorescent dyes for the detection of unfolded proteins in cells. She continued her research under Dr. Yuning Hong at La Trobe Institute for Molecular Science in late 2016. Tracey went on to complete her Master of Biochemical Engineering degree at the University of Melbourne in 2020, where her project was focused on the use of antibodies in current drug delivery systems. Now, she is currently undertaking her PhD under Dr. Manuela Jörg's group at the Monash Institute of Pharmaceutical Sciences. Her research interest is on the development of fluorescently labelled pharmacological tools, with specific focus on the use of dual-functionalized fluorophores in antibody delivery systems.

Development of Dual-Functionalized Fluorophores to Monitor Antibody-Drug Conjugates

Antibody-based therapeutics are paragons in the present era of precision medicine, yet still pose challenges including off-target cytotoxicity and adverse reactions, due to the sub-optimal pharmacokinetics of the antibody and its tendency to accumulate non-specifically in the tumour. These shortcomings result in either low treatment rate of tumours or inaccurate indications of the tumour size, which compromises patient survival or has an incorrect treatment regimen. Consequently, the integration of fluorescence imaging holds promise in providing real-time, precise localization of areas of interest. Here, we report a novel class of click chemistry-dependent switch-on fluorescent probes, comprising of two orthogonal chemical handles that offer utility in click-to-release drug delivery systems based on antibody conjugates. Through photophysical and biological investigations, we have established the applicability of naphthalimide-based tetrazine probes in antibody bioconjugation and imaging, showcasing an 85-fold turn-on response in situ in various fold excess of trans-cyclooctene. The findings highlight the potential of dual-functionalized fluorophores in monitoring other relevant antibody-drug conjugates, paving the way for enhanced therapeutic strategies.

Michael Mah

PhD Student (4th Year) | DDB | Supervisors: Dr. Sarah Turpin-Nolan, Prof Mark Febbraio

Contribution of intestinal ceramides to whole-body metabolic dysfunction

Circulating ceramides, a family of lipids composed of a sphingosine and a fatty acid, are reportedly modulated by diet and are thought to influence the risk, incidence, and/or severity of metabolic diseases. The precise mechanism by which intestinal-derived ceramides are transported to the bloodstream is unclear but is thought to be mediated by gut lipoproteins. We hypothesised the gut-lymph axis of ceramide synthesis and export is a key mechanism that contributes to whole-body metabolic dysfunction. We sought to investigate the metabolic consequences of a species-specific manipulation of gut ceramides via genetic targeting of Ceramide Synthase 2 (CerS2) which is thought to be metabolically protective.

Male Sprague Dawley rats were fed a control, or high-fat diet (HFD) for 7 weeks. The efferent mesenteric lymphatic duct was cannulated to assess the lipidomic signature of lymph-derived chylomicrons. Next, we generated an inducible transgenic mouse that conditionally overexpresses intestinal CerS2. Littermate controls and transgenic CerS2 mice received control, or HFD for 10 weeks. Glucose and lipid metabolism were assessed pre-, and post-, genetic activation. Mice were sacrificed at 16-17 weeks of age, and tissues collected for lipidomic analysis. Whole-mesenteric lymph and chylomicrons were enriched in sphingolipids, and metabolically toxic shorter-chain ceramides were elevated with HFD. Intestinal epithelial cells exhibited a similar profile distribution of ceramides and HFD had a modest effect on short-chain ceramide accumulation. In HFD-fed transgenic mice, intestinal overexpression of CerS2 increased long-chain ceramide synthesis and lowered toxic C16:0 ceramides in the gut. This led to improvements in whole-body glucose metabolism and insulin sensitivity. Short-chain ceramide flux from the intestine is mediated by intestinal chylomicrons via gut-lymphatic channels. Intestinal CerS2 overexpression exerts protective effects on systemic glucose control.

Yining Xie

PhD Student (2nd Year) | D4 | Supervisors: A/Prof Natalie Trevaskis

Hello, I am Yining Xie, a PhD student from D4 Theme, Trevaskis lab. My project is delivering the serine protease inhibitor, dabigatran and its derivative prodrugs, to lymph to treat Acute and Critical illness.

A lipid-based formulation facilitates lymphatic uptake of a protease inhibitor.
Dabigatran etexilate (DABE) is a lipophilic prodrug of dabigatran which is a protease inhibitor that inhibits both trypsin and thrombin and is used clinically as an anticoagulant. Recently, pancreatic protease such as trypsin in the gut-lymph have been shown to promote organ failure in acute and critical illness (ACI). Most drugs access the gut-lymph in low quantities as they are rapidly transported away from the intestine via the blood. Here, we aimed to deliver DABE directly to the gut-lymph to inactivate proteases and potentially offer a targeted therapeutic strategy for organ failure in ACI. A series of lipid-based formulations (LBF) were designed and tested in vitro for their potential to self-emulsify, solubilise DABE and remain stable over time by ensuring the LBF maintained self-emulsification properties and that DABE remained stable without undergoing hydrolysis. In vitro conversion studies were performed to assess the stability of DABE and its conversion to dabigatran under simulated gastrointestinal digestion conditions and in plasma/lymph samples. Ultimately, a Type III A LBF with high self-emulsifying ability of DABE was chosen for progression into in vivo studies in male Sprague Dawley rats to confirm the lymphatic uptake and plasma pharmacokinetics. DABE demonstrated rapid conversion to both an intermediate compound BIBR1087 and dabigatran, both in vitro and in vivo in plasma/lymph. The main species present in both plasma and lymph in vivo was dabigatran and mass transport in lymph of DABE and dabigatran was minimal (~0.5% of dose). Importantly, the concentration of DABE in lymph was substantially higher than in plasma supporting that if the prodrug were stable and did not rapidly convert to dabigatran it would be lymphatically transported. Future studies will investigate strategies to enhance the stability of the prodrug during absorption and optimise the formulation for improved lymphatic uptake.

Lailaturrahmi @aminocte

PhD Student (1st Year) | PPSEd | Supervisors: Dr Ian Larson, Dr Suzanne Caliph, Dr Thao Vu

Lailaturrahmi is a PhD student in Pharmacy and Pharmaceutical Science Education (PPSEd) theme. She is a pharmacist and a pharmacy academic at Universitas Andalas, Indonesia. Her research project is supervised by Dr Ian Larson, Dr Suzanne Caliph, and Dr Thao Vu. The research topic is clinical pharmacy skills and online learning in the Indonesian context, which will focus on desired outcomes, implementation, and impacts of online learning of core clinical pharmacy skills on the involved stakeholders. Her presentation in this symposium covers her experience in applying a scoping review methodology to explore online learning in health professions education.

Exploring online teaching and learning in health professional education: a scoping review.
Online learning has been widely used in health professions education since the last two decades. This study aims to enable better understanding of how online teaching and learning activities are implemented in a health professional education context. The overarching review question for this study is What is the nature of evidence on online learning in health professions education? The scoping review framework by Levac et al. is applied in this review. The framework consists of six stages: 1) identifying the research question, 2) identifying relevant studies, 3) selecting studies, 4) charting the data, 5) collating, summarizing, and reporting the results, and 6) consultation with stakeholders. The inclusion and exclusion criteria are established. The included studies are classified and analysed for the research design, applied theory, online teaching approaches, knowledge, skills, and behaviours taught, online teaching purposes, and learning outcomes. The study also examines the barriers and enabling factors of online teaching and learning from the studies included. The results will be reported using the PRISMA extension for Scoping Review (PRISMA-ScR) checklist. The most significant findings of this study will include identification of various online teaching and learning approaches and pedagogies applied in health disciplines including pharmacy, medicine, nursing and health sciences to develop graduates' knowledge skills and competencies. In addition, the findings will also highlight the enablers and barriers of various instructional approaches and relationship between instructional design and student satisfaction, engagement and learning outcomes.

Imesha Lakmini Hettige

PhD Student (2nd Year) | MedChem | Supervisors: Prof Martin Scanlon

Imesha completed a BSc (Honours in Chemistry) at the University of Sri Jayewardenepura, Sri Lanka, and a Graduateship in Chemistry at the Institute of Chemistry Ceylon, Sri Lanka. She has always been passionate about the world of drug discovery and so chose to pursue a PhD in Medicinal Chemistry at MIPS, under the supervision of Prof. Martin Scanlon and A/Prof. Ben Capuano, in 2022, to gain the skills to become an efficient medicinal chemist. Her current research focuses on developing new chemical tools to understand the biology of fatty acid-binding proteins using fragment-based drug design approaches.

Developing new chemical tools to understand the biology of fatty acid binding protein 4.

Fatty acid-binding proteins (FABPs) are a family of small, water-soluble proteins. They play a complex role in the body including trafficking of lipids, drugs and hormones and have been linked to diseases with aberrant lipid utilisation.

FABP4 is expressed in several tissues, mainly adipocytes and macrophages. FABP4 knockout studies in mice have identified that knockout results in benefits for inflammatory diseases including diabetes and atherosclerosis, indicating that compounds that bind to FABP4 could be valuable therapeutics for metabolic disorders. However, the molecular mechanisms by which FABP4 exerts its biological effects are not fully understood. High-affinity ligands that have been developed against FABP4 have a number of limitations, including high lipophilicity, poor water solubility and off-target activity, making them poor probes to study FABP4 activity in cells. Accordingly, this project aims to develop high-affinity FABP4 selective ligands with good physicochemical properties to aid the investigation of FABP4's role in disease.

A fragment screen conducted within the group identified a novel biaryl N-phenylimidazole fragment (MFP-0000962) as an FABP4 binder. This fragment and its analogues have been utilized in an integrated workflow of microscale parallel chemistry and off-rate screening by Surface Plasmon Resonance (SPR) to develop higher affinity fragments. The chemical libraries of these fragments are designed to explore diverse three-dimensional pharmacophores at specific positions on the fragment core. A suite of biophysical tools including SPR, Isothermal Titration Calorimetry (ITC), NMR and X-ray crystallography are used to characterize the analogues that bind with the highest affinities for the ongoing design.

Hefeng Song

PhD Student (1st Year) | D4 | Supervisors: A/Prof Natalie Trevaskis

My name is Hefeng Song and I'm a first year PhD student from Drug Delivery Disposition and Dynamics. I finished my Honours study last year in Trevaskis lab and investigated the potential of two different transdermal corticosteroid delivery approaches on osteoarthritis treatment. I continued my PhD study in Trevaskis lab, exploring obesity-associated changes on meningeal lymphatics.

Novel approaches to deliver betamethasone dipropionate for hand osteoarthritis treatment

Hand osteoarthritis (OA) is a prevalent condition characterized by joint pain and loss of function. While current treatments of oral and injected corticosteroids have demonstrated some effectiveness in hand OA, their limitations, including adverse systematic effects and patient discomforts can be problematic. Transdermal drug delivery (TDD) offers the advantages of minimized systemic effects, reduced discomfort, localized treatment and improved patient accessibility, making it a promising alternative for the hand OA management. However, stratum corneum (SC), the skin's outermost layer, presents a significant barrier for TDD. Both physical and chemical approaches were developed to achieve temporary SC barrier disruption. Microneedle (MN) patch (provided by Voelcker's group) can create physical pathways for drug to penetrate whereas evaporative solvent-based formulation has permeation enhancers and anti-nucleation polymers to achieve drug supersaturation on the SC and facilitate drug absorption. Betamethasone dipropionate (BDP), a highly potent corticosteroid has been selected as the drug of interest for its potential to penetrate the SC. In this study, a sensitive liquid chromatography with tandem mass spectrometry (LC-MS/MS) method was used for BDP quantification in formulations and in in vitro skin diffusion studies (Skin-Parallel Artificial Membrane Permeability Assay (PAMPA) and Franz Diffusion Cells). Complementary, BDP distribution in the porcine skin tissue was visualized using Matrix Assisted Laser Desorption/Ionization Mass Spectrometry Imaging (MALDI MSI). The results indicated that the choice of formulation components had certain impact on BDP permeation. The solutions showed no significant penetration through the tested membranes (Strat-M and porcine skin), while the MNs enhanced drug penetration on both membranes comparing to solutions. Future studies, including in vivo studies and potentially in clinical trials, are needed to determine whether the amount of BDP delivered through the skin is efficacious for hand OA treatment as well as to evaluate the safety and therapeutic outcomes of the novel BDP delivery approaches for patients.

Travis Lay linkedin.com/in/travis-lay96/

PhD Student (3rd Year) | MedChem | Supervisors: Dr David K Chalmers

Travis Lay completed a Bachelor of Pharmaceutical Sciences in 2018 at Monash University. After graduating, he spent some time working at Aspen Pharmacare. In 2020, he returned to Monash university to undertake his honours degree under the supervision of Dr. David Chalmers. Following the completion of this degree, he chose to pursue his PhD in Medicinal Chemistry. Currently in the 3rd year of his PhD, Travis' work focusses on modifying peptides to improve their oral delivery and enhance their therapeutic potential.

Marrying Activity with Permeability Towards Orally Bioavailable Somatostatin Peptide Therapeutics

Peptides are effective pharmaceutical agents. However, their therapeutic potential is limited by their lack of oral bioavailability. Orally active drugs need to simultaneously be metabolically stable, membrane permeable and active against a drug target. This trifecta is difficult to achieve for peptides. A well-known example of a peptide that is orally active without formulation enhancements is cyclosporin A (CSA) and is often cited as proof of concept that oral peptides are possible. Although developing peptides that are active and metabolically stable is challenging, membrane permeation remains the limiting factor in oral peptides. Previous works on peptide permeability have established features that enhance membrane permeation such as cyclisation or reduction of hydrogen bonds. However, these studies have been applied to non-bioactive peptides. Hence, the challenge remains in designing more drug-like peptides by incorporating chemical characteristics that favour membrane permeability whilst maintaining acceptable metabolic stability and activity against a target. Somatostatin receptors are well-studied drug targets that are modulated by cyclic peptides. This GPCR family is responsible for diverse physiological functions such as hormone regulation. Peptide therapeutics targeting somatostatin exist as injectables. Patient compliance would be greatly improved by developing an orally bioavailable peptide analogue. In this work, we aim to improve the membrane permeability of previously reported, bioactive somatostatin analogues by applying established rationales. Permeability of our analogues are modelled using the parallel artificial membrane permeability assay (PAMPA). Binding of peptides are also measured through a binding assay. Computational models are used to rationalise the permeability of the designed peptides.

Asuka Takanashi

PhD Student (3rd Year) | D4 | Supervisors: Prof. Colin Pouton

Delivery and expression of LNP mRNA in the secondary lymphoid organs drive robust immune responses

Lipid nanoparticles (LNPs) are the prime delivery vehicle for mRNA vaccines. Previous hypotheses suggested that LNPs contribute to innate reactogenicity and lead to the establishment of a vaccine adaptive response. It has not been clear whether LNP adjuvancy in the muscle is the prime driver of adaptive immune responses or whether delivery to secondary lymphatic organs is necessary to induce strong adaptive responses. To address this, we formulated reporter gene (NLuc) or OVA mRNA into LNP or coadministered the mRNA with empty LNP. After IM injection, we correlated the delivery with adaptive immune responses. Additionally, we investigated humoral responses to modified mRNA encoding the SARS-CoV-2 spike protein. Compared to unformulated mRNA encoding nanoluciferase, with or without co-administered empty LNPs, LNP-formulated mRNA resulted in high levels of nanoluciferase in the secondary lymphoid organs. Similarly, LNP-mRNA encoding ovalbumin led to a cellular immune response against OVA while free mRNA, with or without empty adjuvanted LNPs, caused little or no immune response. Finally, only mice injected with LNP-formulated mRNA encoding SARS-CoV-2 spike protein elicited robust cellular and humoral immune responses. Our results suggest that the mRNA delivery and transfection of secondary lymphatic organs, not LNP adjuvancy or RNA expression in muscle, are the main drivers for adaptive immune response in mice. This work informs the design of next-generation mRNA delivery systems where better delivery to secondary lymphatic organs should lead to a better vaccine response.

Thien Nhan Lu

PhD Student (3rd Year) | MedChem | Supervisors: Prof. Peter J. Scammells and Assoc. Prof. Sheena McGowan

The development of dual PfA-M1 and PfA-M17 inhibitors via computational approaches

Malaria remains a global health threat owing to the emergence of drug-resistant parasites. Plasmodium falciparum M1 and M17 aminopeptidases (PfA-M1 and PfA-M17) are attractive antimalarial drug targets for discovering novel compounds that can control malaria by inhibiting hemoglobin digestion. Hydroxamates are known to inhibit both PfA-M1 and PfA-M17, yet the most potent derivative has moderate aqueous solubility. Here, we report our investigation of a series of hydroxamates using three two-dimensional quantitative structure–activity relationship (2D-QSAR) models in combination to predict the enzymatic inhibition of PfA-M1 and PfA-M17 and their antimalarial activity against Pf-3D7 parasites. The AutoDock Vina program was validated as the best molecular docking tool for high-throughput virtual screening of the new hydroxamates and for elucidating the experimental process. An alanine virtual scan was first employed to identify the key residues of PfA-M1 and PfA-M17 with which the new hydroxamates would need to interact to retain the dual inhibition of these enzymes. In combination, the 2D-QSAR models, molecular docking, and alanine virtual scan models enabled us to estimate the biological activities of the new hydroxamates with relatively high accuracy before selecting them for synthesis. With our initial results on PfA-M17, two compounds, MIPS3922 and MIPS3943, were firstly synthesized and exhibited potent inhibition toward PfA-M17 with Ki values of 134 ± 30 and 113 ± 26 nM, respectively, compared to the most antiparasitic activity and dual PfA-M1 & PfA-M17 inhibitor MIPS1778 with a Ki value of 260 nM toward PfA-M17.

Cameron Fairweather

PhD Student (4th Year) | DDB | Supervisors: Dr Tracy Josephs

RAMP it up! Exploring conformational dynamics of the amylin 3 receptor (AMY3R) using HDX-MS

Amylin is a peptide hormone expressed in the pancreas, serving as a key satiation signal that moderates gastric emptying and enhances energy expenditure. The amylin 3 receptor (AMY3R) represents one of the primary sensors for the amylin peptide and is, therefore, a focal point for therapeutic interventions in metabolic conditions such as diabetes and obesity. AMY3R is a heterodimer, composed of the class B GPCR calcitonin receptor (CTR) and receptor activity-modifying protein 3 (RAMP3). While recent cryoEM structures of AMY3R and other amylin receptor subtypes have illuminated details of peptide and G protein engagement, a comprehensive understanding of how distinct receptor subtypes and peptide ligands manifest distinct pharmacological properties remains elusive.

To gain deeper insights into the molecular mechanisms governing AMY3R pharmacology, we leveraged hydrogen deuterium exchange mass spectrometry (HDX-MS) to investigate the conformational dynamics of AMY3R in the apo (unbound) state and when bound to two therapeutically relevant peptide agonists: rat amylin (rAmy) and salmon calcitonin (sCT). Comparing the unbound and the two peptide bound states, we observed that both peptides reduced deuterium uptake in both the CTR and RAMP3 extracellular domains, suggesting reduced overall dynamics in this region. Conversely, peptide binding appears to increase the dynamics of the RAMP3 transmembrane domain, evidenced by increased deuterium uptake in this region. Comparing the rAmy and sCT bound states, we observed several interesting differences. In transmembrane helix 6 (TM6) and extracellular loop 3 (ECL3) of CTR, sCT bound AMY3R had markedly reduced deuterium uptake compared to the rAmy bound state, particularly at later time points. Similarly, sCT conferred greater protection than rAmy at intracellular helix 8, which forms key contacts with G proteins. Collectively, our results provide molecular insights into the changes in dynamics that occur upon peptide binding to AMY3R, as well as a structural basis for the pharmacological profiles of rAmy and sCT.

Katayoun Nazemi

PhD Student (2nd Year) | D4 | Supervisor: Assoc. Prof John F. Quinn

I am Katayoun Nazemi and I received my MSc degree in Biomedical Engineering. I joined the Monash Institute of Pharmaceutical Sciences as a Ph.D. student in 2021, and my current research focuses on new redox-active materials for manipulating cell signaling processes. I work on synthesizing macromolecules Hydrogen sulfide (H2S) donors which can liberate H2S when triggered by thiol-containing compounds.

New redox-active materials for manipulating cell signaling processes

Hydrogen sulfide (H2S), the most recently discovered of the gasotransmitter molecules, plays a crucial role in mediating many biological processes, and may have therapeutic utility for disorders associated with intracellular redox imbalance. Macromolecular H2S donors are promising H2S delivery systems due to their tunable physical and chemical features. To this end, a library of copolymers were synthesized using reversible addition-fragmentation chain-transfer (RAFT) polymerization. The synthesis was carried out using different molar stoichiometries of oligo(ethylene glycol) methyl ether methacrylate (Mn 300 g·mol − 1 (OEGMA300), and Mn 500 g·mol − 1 (OEGMA500), and vinyl azlactone (VDM). VDM was used as a reactive platform for post-polymerization modification, allowing modification of the side-chains with cholesterol-trisulfide moieties. Cholesterol-trisulfide amide conjugation can lead to H2S release via thiol-exchange reactions, and also to generation of persulfides. For polymer 1 (EV1), the ring-opening reaction with a cholesteryl-trisulfide-amine was monitored using FT-IR. The signal at 1813 cm-1 associated with the C=O stretch in the VDM disappears following conjugation, indicating successful conjugation. Furthermore, the 1H NMR spectrum shows characteristic peaks of cholesterol-trisulfide, with appropriate integration values to confirm successful ring-opening of the azlactone groups. Self-assembly of the polymers was investigated using dynamic light scattering.

Sarah Yang SarahSHYang

PhD Student (3rd Year) | PPSEd | Supervisors: A/Prof Elizabeth Yuriev, A/Prof Jennifer Short

Sarah Yang is a third year PhD student from the Pharmacy and Pharmaceutical Sciences Education theme. Her research area of interest is in the training of instructors, particularly sessional teaching associates, for online teaching. The outcomes of this study will provide an enhanced understanding and allow for the creation of clear guidelines for developing the skills of online facilitators which will benefit the online learning community both locally and internationally. Prior to starting PhD, Sarah completed Bachelor of Pharmacy, Bachelor of Pharmaceutical Science (Honours) and Master of Pharmacy Practice at Monash University and is a registered community pharmacist.

Teaching associates' perspectives of online teaching and learning in a pharmaceutical science degree

During COVID-19, the synchronous Zoom™ meeting breakout rooms with Google Docs™ replaced the face-to-face workshops in the Bachelor of Pharmaceutical Science (BPharmSci) degree at Monash University. However, due to the abrupt transition, an understanding of the effective facilitation approaches in such setting was lacking. This project aims to identify approaches used by teaching associates (TAs) to facilitate small synchronous workshop-style online classrooms and to analyse their perspectives of online education. Seven TAs teaching into the first year BPharmSci degree were observed in their online classrooms and semi-structurally interviewed. A frequency analysis approach (counting the number of times a particular, known effective facilitation strategy used) and the reflexive thematic analysis approach were used to analysis the data respectively. The observation data revealed that the TAs used a wide range of facilitation approaches that are known to be effective, where the most frequently used approaches included lecturing, questioning, listening, and providing feedback. Zoom features were also employed, namely moving between breakout rooms followed by sharing screen. The interview analysis showed that setting expectations and having a structured workshop with judicious group formation and instructor-prepared Google Docs were considered effective. However, non-compulsory and/or non-assessed classes and student-prepared Google Docs were perceived as less effective. Identified improvement areas included promoting camera use

during class, holding TA briefings earlier to allow more preparation time, and expanding online facilitator training. Barriers to improvement were also revealed, such as students' unfamiliarity with peers and a delayed facilitator notes availability. The former discouraged students' camera use during class while the latter led TAs to feel under-prepared.

Liam Hales @LiamHalesMIPS

PhD Student (3rd Year) | MedChem | Supervisor: Prof Philip Thompson

Liam completed a Bachelor of Pharmaceutical Science (Advanced Honours) in 2019 at Monash University. Having enjoyed the challenge of the Honours research environment, he chose to pursue a PhD in Medicinal Chemistry under the guidance of Prof. Phil Thompson at MIPS. Currently in the 3rd year of his PhD, his work focuses on the exciting field of Targeted Protein Degradation, particularly on molecules known as PROTACs. His goal is to improve the efficiency of their synthesis and harness their potential to help treat diseases such as Hepatitis B.

HARNESSING SOLID PHASE SYNTHESIS IN THE PURSUIT OF PROTEIN DEGRADERS

Developing straightforward but flexible approaches to PROTAC synthesis that can incorporate the structural elements of emerging designs can improve the quality and efficiency of PROTAC development. Solid-phase approaches could offer many advantages over conventional PROTAC synthesis if diverse chemistries and topographies can be incorporated. We have exploited the backbone-amide-linked (BAL) resin to employ an array of solid-phase organic reactions, providing access to VHL- and IAP-targeting degraders using the BRD4-targeting JQ1 conjugates as examples.

Karoline Sanches

PhD Student (3rd Year) | MedChem | Supervisor: Ray Norton and Martin Scanlon

I am a Bacharel in Biological Physics from UNESP/Brasil and Master of Science in Molecular Biophysics from UNESP/Brasil. Currently, I am a PhD candidate at Monash Institute of Pharmaceutical Sciences under the supervision of Ray Norton where I am studying the molecular basis of Kv1.3 inhibition through NMR, molecular dynamics simulations among other biophysical techniques.

ShKT-Ts1, a novel peptide from the sea anemone *Telmatactis stephensoni*: Studies of the structure-function relationship in ShKT domain peptides

The ShKT is a common scaffold in sea anemone peptides, first found in a toxin from Stichodactyla helianthus. 1 The ShK-186 (Dalazatide), an ShK analogue, has completed Phase 1 clinical trials to treat plaque psoriasis. 2 Although the ShKT are found in numerous species, only a tiny fraction have been functionally characterised, with some ShKT peptides from sea anemones inhibiting K V 1.x, others do not. 3, 4 The K V 1.x blockade is mediated by a Lys-Tyr (KY) dyad, but other cationic followed by a hydrophobic residue may also be relevant, but not necessarily guarantee their activity to block those ion channels. 5 In this work, we used NMR and MD simulations to predict the potential activity of the novel ShKT peptide, the ShKT-Ts1. We solved the 3D solution structure of ShKT-Ts1 and performed functional essays against a range of K V 1.x channels. Although ShKT-Ts1 has an ShK-like fold and a Lys-Phe dyad, it does not show significant activity against K V 1.x channels. With MD simulations, we investigated whether solvent exposure of the dyad residues may be informative in rationalising and potentially predicting the ability of ShKT peptides to block K V 1.x channels. We propose a relationship between the extent of solvent exposure of the dyad, peptide dynamics and activity against K V 1.x, with channel-blocking activity depending on the exposure of the dyad. The presence of buried or partially exposed dyads that are buried during MD simulations correlates with weak or absent activity against K V 1.x channels. Therefore, structure prediction, coupled with MD simulations, can be used to predict whether new sequences belonging to the ShKT family may act as potassium channel blockers.

Adam Livori @cardiopharmnerd

PhD Student (2nd Year) | CMUS | Supervisors: Prof Simon Bell, Prof Zanfina Ademi, Dr Jedidiah Morton

Adam Livori is a cardiac clinician researcher currently completing his PhD in pharmacoepidemiology, health economics and translational science. He works clinically as consultant cardiology pharmacist at Grampians Health, overseeing medical specialties and ambulatory care in cardiology. His research interest includes applied biostatistics and health economic analysis. His passionate about open-source science and currently holds research funding under Safer Care Victoria, and collaborates between CMUS and the Victorian Heart Institute. His PhD title is "Patterns and predictors of clinical outcomes in myocardial infarction and atrial fibrillation.

Revascularization and medication use following NSTEMI: analysis of 15,339 admissions in Victoria

Aim

Clinical practice guidelines recommend secondary prevention medications post myocardial infarction (MI) regardless of revascularization strategy. Preliminary evidence suggests there is variation in post-MI medication use between patients who undergo percutaneous coronary intervention (PCI) and coronary artery bypass grafts (CABG). The objective of this study was to investigate patterns of 12-month post-MI medication use according to revascularization strategy following non-ST elevation myocardial infarction (NSTEMI).

Methods

We included all admissions for NSTEMI in Victoria, Australia, between July 2012 and June 2017. We investigated dispensing of P2Y12 inhibitors (P2Y12i), statins (total use and high-intensity only), ACE inhibitors or angiotensin receptor blockers (ACEI/ARBs), and beta-blockers within 60 days post-discharge. Medication use was estimated as the proportion of days covered (PDC) over a 12-month period from the date of hospital discharge . Analyses were performed using adjusted parametric regression models stratified by revascularization strategy during admission or within 30 days of hospital discharge .

Results

There were 15,399 admissions for NSTEMI – 11,754 with PCI and 3,645 with CABG. Following co-variate adjustments, predicted probability of dispensing for PCI and CABG were 94% (93-0.95%) vs. 17% (13-21%) for P2Y12i; 69% (66%-71%) vs. 43% (38-49%) for ACEi/ARB; 59% (57-62%) vs. 69% (64-74%) for beta blockers; 89% (87-89%) vs. 89% (86-92%) for statins; and 60% (57-62%) vs. 69% (63-73%) for high intensity statins, respectively.

Conclusions

Variance in the use of secondary prevention medications was not uniform across all classes with respect to revascularization strategy. There is a demonstrated need for interventions in ensuring improved utilization of medications post-discharge.

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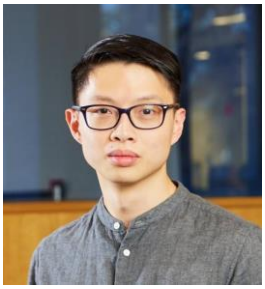

PhD Student (3rd Year) | MedChem | Supervisors: Prof. Martin Scanlon

Jason Pun completed his bachelor of pharmaceutical sciences degree with a medicinal chemistry major, having undertaken research projects under the supervision of Prof. Bernard Flynn and Prof. Martin Scanlon. Jason is currently in his third year of PhD with the Scanlon group with a focus in the design and synthesis of novel chemical probes for metabolic diseases such as type 2 diabetes and atherosclerosis. He's also interested in data science and cheminformatics. More specifically, he's working on developing computational tools to better guide early medicinal chemistry efforts in fragment-based drug discovery campaigns.

Fragment-based development of chemical probes for FABP4

Fatty acid binding proteins (FABPs) are a family of proteins that are synonymous with the transport of poorly water-soluble ligands, but it is becoming increasingly apparent that they play more important roles in facilitating various signalling pathways. FABP4-knockout mice have been shown to be resistant to diabetes and atherosclerosis, although the detailed mechanisms that underpin this phenotype remain unclear. Thus, there is a need for potent and highly selective chemical probes to interrogate the molecular mechanism of

FABP4.

Previous work within our group identified a diverse set of fragment hits against FABP4. These hits were validated using multiple orthogonal assays, and their developability assessed by screening commercially available analogues. Ongoing work is underway to elaborate two chemical series into more potent and selective binders through structure-based drug design, and screening of libraries of analogues prepared through plate-based parallel microscale synthesis.

In this work, libraries of analogues have been synthesised using reagent sets designed to maximally explore chemical diversity along a vector of expansion. The crude reaction mixtures were screened using the an off-rate screening (ORS) by surface plasmon resonance (SPR) workflow. Subsequent resynthesis and validation have identified compounds improved affinity, which are currently being evaluated in cell-based assays. In addition, the process of ORS data analysis and hit selection is being re-evaluated to expand analysis methods and identify opportunities to improve reliability and validation rates.

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PhD Student (3rd Year) | D4 | Supervisors: A/Prof Joseph A Nicolazzo and Dr Liam Koehn

Showmika Supti is a 3rd year PhD student at the Drug Delivery, Disposition, and Dynamics department of Monash Institute of Pharmaceutical Sciences (MIPS). Her PhD project aims to understand the impact of iron and ApolipoproteinE (ApoE) status on fatty acid trafficking across the blood-brain barrier. Her project is under the supervision of Associate Professor Joseph Nicolazzo and Dr Liam Koehn. She is also the recipient of Sir John Monash Medal (2018), which is awarded to one graduating student each year for academic excellence and to have demonstrated a significant commitment, while at Monash University, to advancing the University's goals of social justice, human rights, and a sustainable environment.

The impact of iron on fatty acid trafficking across the blood-brain barrier

Alzheimer's disease (AD) is characterised by hallmark features such as amyloid-beta (Aβ) accumulation, neurofibrillary tangles formed by hyperphosphorylated tau, brain atrophy and sustained neuroinflammation. Apart from these hallmarks, a reduction in docosahexaenoic acid (DHA) has also been observed in the brain of people with AD. The de novo synthesis of DHA in the brain is limited. Hence plasma-derived DHA has to be transported across the blood-brain barrier (BBB) to maintain healthy brain DHA levels. There is plenty of evidence demonstrating the effects of iron on the pathology of AD but limited understanding of its impact at the BBB. The data from the present study are the first to demonstrate that increasing intracellular iron levels using ferric ammonium citrate (FAC) led to a 22% downregulation of fatty acid transporter protein (FATP1) at the protein level (via western blot) but not the mRNA level on human cerebral microvascular endothelial (hCMEC/D3) cells. Furthermore, upon performing functional studies it was observed that FAC had no impact on the uptake of 3H-oleic acid (3H-OA) and 14C- DHA but FAC significantly impacted on the efflux of 3H-OA and 14C- DHA from the hCMEC/D3 cells at various timepoints. While further studies are required to elucidate the molecular mechanisms underlying the FAC-induced downregulation of FATP1, these studies provide insight into a role of iron in regulating FATP1 at the BBB, which may have implications on the transport of fatty acids to and from the brain.

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PhD Student (3rd Year) | PPSEd | Supervisor: Prof Paul James White

I am Adeladlew Kassie Netere, a PhD. student at Monash University, Faculty of Pharmacy and Pharmaceutical Sciences, specializing in education research. My primary focus is on developing and validating pharmacology concept inventory instruments. I aspire to delve into Methodologies and Approaches utilized in the development and validation processes of educational assessment tools (EAT). My passion lies in advancing research-based learning assessment tools for measuring student understanding and informing educational decisions. I aim for a career in academia to further improve our comprehension of learning outcome quality assurance guidelines and enhance the effectiveness of educational assessment tools.

Concept Inventory Development: A Comprehensive Systematic Review of Methodologies and Approaches

Introduction: In education, Concept Inventories (CIs) serve a vital role by rigorously assessing students' understanding of key concepts, aiding educators in their instructional choices, and promoting educational progress. However, the lack of standardized methodologies for CI development can limit their effectiveness and broader adoption. This study aims to address this issue by constructing an evidence-based model for CI development through an extensive review of existing instruments and validation techniques.

Methods: Our systematic search covered six electronic databases, followed by a preliminary literature review to structure the data extraction format. We applied a theoretical and inductive thematic analysis approach, complemented by expert discussions, for the data extraction and analysis process
Results: In total, 97 articles were analyzed, resulting in the formulation of an iterative five stages model for CI development. These stages encompass concept selection and validation, misconception identification, item formation, item validation, and tool application and refinement. Additionally, we stratified and described various psychometric properties applied in CI tool validation, shedding light on their contributions to the validation process.
Conclusion: This research underscores the growing interest in using CI instruments to evaluate educational decisions and learning outcomes, emphasizing the need for a standardized development model. The proposed five-stages model offers a structured framework to enhance CI development, while the described validation process can aid in assessing the reliability of CI tools. Future endeavors should focus on creating comprehensive CI quality assurance guidelines to optimize the efficacy of educational assessment tools, bridging gaps, and promoting a cohesive evaluation approach.

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PhD Student (3rd Year) | MedChem | Supervisors: Prof. Martin Scanlon, A/Prof. Ben Capuano

Jeyan completed his bachelors of pharm. sci. (maj. med. chem.) in 2018, at MIPS. He then stayed on for an honours degree within the drug delivery theme, where he worked on photo-responsive anti-bacterial drug release from porous silicon nanoparticles under supervision of Dr. Bo Peng and Prof. Nicolas Voelcker. Now, he is in his final year of PhD with a focus on developing synthetic and analytical methods for accelerating PROTAC discovery within the medicinal chemistry theme, under the supervision of Prof. Martin Scanlon and A/Prof. Ben Capuano.

Accelerating PROTAC discovery

Proteolysis targeting chimeras (PROTACs) are small molecules that hijack the ubiquitin proteosome system in order to label proteins of interest (POI) for degradation. PROTACs are comprised of a POI binder and an E3 ligase recruiting element (E3RE) that are covalently tethered by a linker. Recent studies have highlighted the importance of the linker's role to afford stable and long-lived ternary complexes. Long-lived complexes appear to be necessary for efficient ubiquitination and degradation.1, 2 Therefore, efficient strategies are required to identify optimal linkers that generate a stable ternary complex. To address this, we have designed diverse library of linkers utilising Tanimoto similarity and pharmacophore diversity metrics, whilst simultaneously enriching for linkers that are found in active PROTACs.3 From this analysis we selected a 43-membered linker library. The library was used to synthesise potential PROTACs in parallel and at microscale (2.5 μmol).4 The products from this parallel synthesis will be screened by surface plasmon resonance (SPR) with minimum work-up an purification. We hypothesis that this will enable dissociating ternary complexes (TC) to be identified via "off-rate screening".5 In this work, the linker library was used to synthesise potential PROTACs with amide coupling chemistry featuring different POI targeting ligands. Two POIs were selected; the well-characterised bromodomain Brd4BD2, as well as fatty-acid binding protein 4.

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