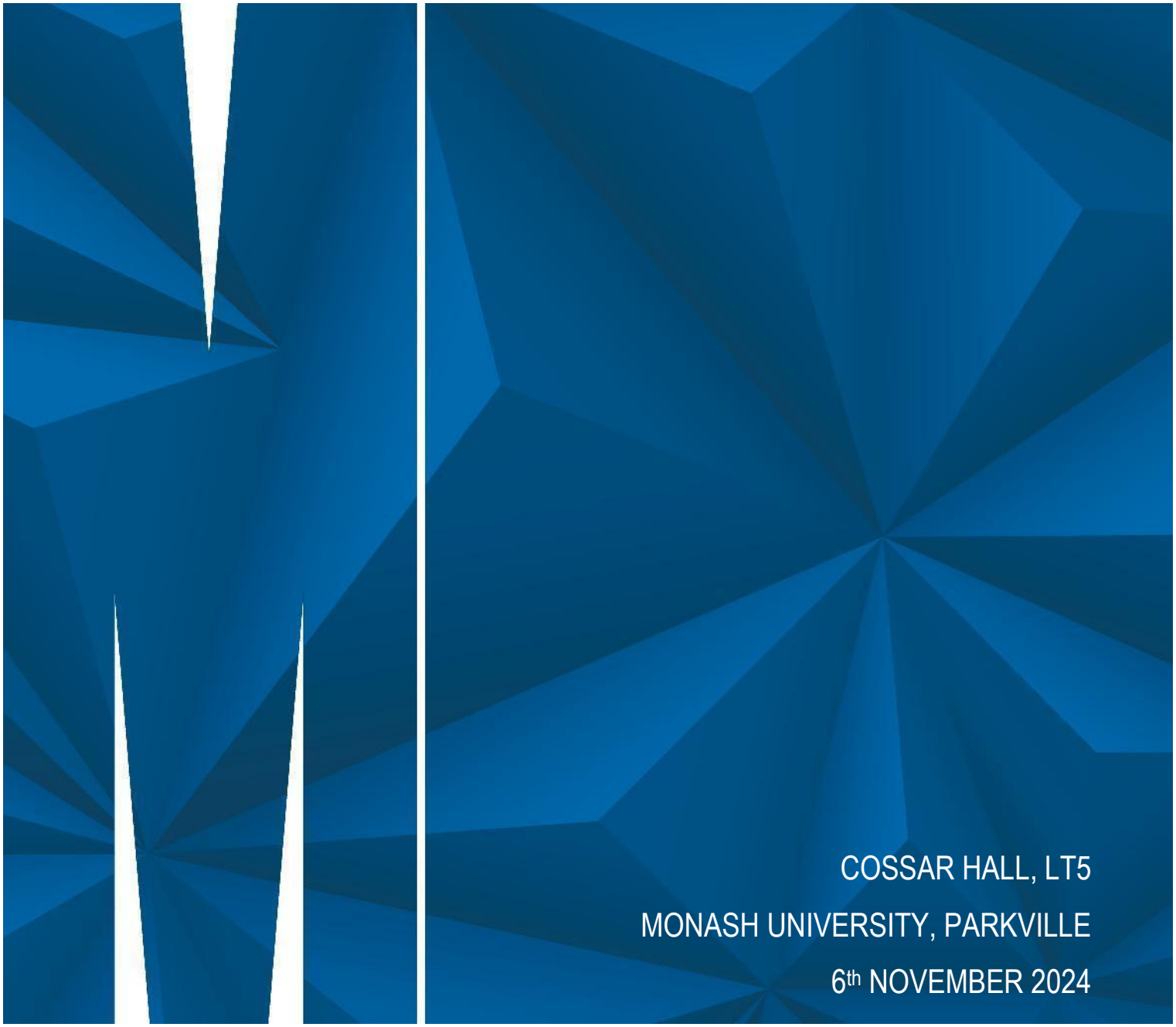
MONASH University

PARKVILLE POSTGRADUATE ASSOCIATION

PHARMACY AND PHARMACEUTICAL SCIENCES

19TH ANNUAL HIGHER DEGREE BY RESEARCH (HDR) SYMPOSIUM 2024



COSSAR HALL, LT5

MONASH UNIVERSITY, PARKVILLE

6th NOVEMBER 2024

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

		SISSONS BUILDING FOYER
8:00 - 8:45 am	**Registration**	
Opening Ceremony		LECTURE THEATRE 5
9:00 - 9:10 am	Symposium Opening Remarks ***Joseph Nicolazzo*** *(Professor and Associate Dean)*	
9:10 - 9:30 am	Run sheet & introducing Keynote speaker ***Bilal and Ali*** (Education officers 2024)	
9:30 - 10:00 am	Keynote Plenary ***Dr. Kathy Nielsen*** *(CEO BioCurate)*	
Oral Presentation Session 1 *Chairs: Bilal and Ali*		LECTURE THEATRE 5
10:00 - 10:15 am	Shining a light on intracellular GPCR signalling using optogenetics. ***Chantel Mastos*** *(DDB)*	
10:15 - 10:30 am	A Comparative Study on Surface-engineered Nanoceria: Colloidal Stability vs. Antioxidant Activity. ***Milad Ghorbani*** *(D4)*	
10:30 - 10:45 am	Developing new chemical tools to understand the biology of fatty acid binding protein 4. ***Imesha Lakmini Hettige*** *(MedChem)*	
10:45 - 11:00 am	Diabetes Medication Recommendations for Older Adults: A Systematic Review of the Western Pacific. ***Darshna Goordeen*** *(CMUS)*	
11:00 - 11:15 am	Revealing the Hidden Face of GPCRs- Mapping Inactive states. ***Minakshi Baruah*** *(DDB)*	
Morning Tea & Poster Viewing		COSSAR HALL
11:15 - 11:50 am	**Morning Tea & Poster Viewing**	
Poster Presentation Session 1: Group A ***(concurrent)***		COSSAR HALL
11:15 - 11:20 am	Deprescribing BZRAs in the elderly and people with cognitive impairment: a systematic review. ***Aisling McEvoy*** *(CMUS)*	
11:20 - 11:25 am	Mathematical model predicts antibiotic effect on Pseudomonas aeruginosa where PK/PD indices cannot. ***Alice Terrill*** *(D4)*	
11:25 - 11:30 am	Education-Related Inequality in Quality-Adjusted Life Expectancy. ***Sheridan Rodda*** *(CMUS)*	
11:30 - 11:35 am	Novel Electrochemical Sensors for Rapid Identification of Carbapenem-Resistant Bacterial Infections. ***Foroogh Rezaei*** *(MedChem)*	
11:35 - 11:40 am	Novel Peptide-Based Inhibitors of Protein Kinase Cε for the Treatment of Type 2 Diabetes Mellitus. ***Abisola Ave-Maria Siedoks*** *(MedChem)*	
11:40 - 11:45 am	The effects of multiple resistance mechanisms on Pseudomonas aeruginosa response to meropenem. ***Dominika Fuhs*** *(D4)*	
Poster Presentation Session 1: Group B ***(concurrent)***		COSSAR HALL
11:15 - 11:20 am	Strategies for generating and translating evidence for better medication management in aged care. ***Annie (Mey Lee) Ea*** *(CMUS)*	
11:20 - 11:25 am	Structure and functional studies of Avt1, a novel peptide from the sea anemone Aulactinia veratra. ***Renad Albar*** *(MedChem)*	
11:25 - 11:30 am	Lipidation of HsTX1[R14A] alters its pharmacokinetics and biodistribution to target tissues. ***Lihuan Lin*** *(D4)*	

11:30 - 11:35 am	Structural understanding of tirzepatide on GIPR and GLP-1R. ***Qinghao Ou*** *(DDB)*
11:35 - 11:40 am	Development of fluorescent protein degraders for bromodomain-containing protein 4. ***Marisa G. Santibanez Moran*** *(MedChem)*
11:40 - 11:45 am	Development of Novel dTAGs to Study Role of Different Proteins. ***Jun Yeob Kim*** *(MedChem)*
Oral Presentation Session 2 *Chairs: Ali & Bilal*	LECTURE THEATRE 5
11:50 - 12:05 pm	Ceftolozane/tazobactam plus meropenem against ST235-clone Pseudomonas aeruginosa isolates in HFIM. ***Siobhonne Breen*** *(D4)*
12:05 - 12:20 pm	Chemical Nose for Discriminating Amyloids in Neurodegenerative Diseases. ***Paulo Simon*** *(MedChem)*
12:20 - 12:35 pm	MHC-II+ TAMs are present in responders of chemotherapy-beta-blocker combination therapy. ***Amir Hossain*** *(DDB)*
12:35 - 12:50 pm	Biomarker Discovery in Parkinson's Disease- a comprehensive look at sphingolipids pathway. ***Ali Esfandiary*** *(D4)*
12:50 - 01:05 pm	Investigating the Neural Control of Goblet Cells. ***Matthew Rowe*** *(DDB)*
Lunch & Poster Viewing	COSSAR HALL
01:05 - 02:00 pm	**Lunch & Poster Viewing**
Poster Presentation Session 2: Group A *(concurrent)*	COSSAR HALL
1:05 - 1:10 pm	Effect of Conjugation Site & Corona Chemistry on the Therapeutic Activity of Nanorod-Drug Conjugates. ***Nicole Warne*** *(D4)*
1:10 - 1:15 pm	Investigating the role of TDP-43 in mitochondrial dysfunction and neurotoxicity. ***Monica Suehiro*** *(DDB)*
1:15 - 1:20 pm	Further uses of hydantoins as directing groups: Palladium-catalyzed C-H amination. ***James Bowers*** *(MedChem)*
1:20 - 1:25 pm	Parasite-Host Metabolic Cross-Talk to Detect Malaria. ***Teha Gebi*** *(D4)*
1:25 - 1:30 pm	Strain-release synthesis of 2-azabicyclo[2.1.1]hexan-3-ones from bicyclo[1.1.0]butanes. ***Nathan Bell*** *(MedChem)*
1:30 - 1:35 pm	"Pain-on-a-Chip" Platform for Discrimination of Various Chronic Pain Types. ***Douer Zhu*** *(D4)*
1:35 - 1:40 pm	Cholesterol-terminated cationic lipidated oligomers (CLOs) as a new class of antifungals. ***Muhammad Bilal Hassan Mahboob*** *(D4)*
1:40 - 1:45 pm	Targeted Protein Degradation: A Novel Target Deconvolution Method. ***Chuhui Huang*** *(MedChem)*
1:45 - 1:50 pm	Trajectory of health-related quality of life of heart failure patients. ***Kuan Wai Chee*** *(School of Pharmacy, Monash University Malaysia)*
1:50 - 1:55 pm	Development of a Malaysian screening tool for potentially inappropriate prescribing in older adults MALPIP): a Delphi study. ***Chang Chee Tao*** *(School of Pharmacy, Monash University Malaysia)*
1:55 - 2:00 pm	The Mechanism of Zerumbone in Mitigating Cellular Ageing: Molecular Targets Identification. **Lee Wen Hwei** *(School of Pharmacy, Monash University Malaysia)*

Poster Presentation Session 2: Group B *(concurrent)*	COSSAR HALL
1:05 - 1:10 pm	Distal C(sp³)-H Amidation via Ind*Rh(III) Catalysed Nitrene Transfer. **Hannah Jane Ross** *(MedChem)*
1:10 - 1:15 pm	Efficient Polymyxin Depsipeptides Synthesis using Solid-Phase, modified Yamaguchi, and NCL. ***Talal Alrubaie*** *(MedChem)*
1:15 - 1:20 pm	Development of selective small molecule chemical probes to investigate FABP5 function. ***Evgenia Konstantinidou*** *(MedChem)*
1:20 - 1:25 pm	Enhancing the Cytosolic Delivery of Bioactive Peptides. ***Kathryn Fincham*** *(MedChem)*
1:25 - 1:30 pm	Disease-related factors affecting P-glycoprotein abundance in brain endothelial cells and microglia. ***Ethan Kreutzer*** *(D4)*
1:30 - 1:35 pm	The development and evaluation of novel hybrid ligands for M4 muscuranic acetylcholine receptors. ***Ya Su*** *(MedChem)*
1:35 - 1:40 pm	Discovery of Potent M1 and M4 mAChR Agonists for the Treatment of CNS Disorders. ***Boqun Liu*** *(MedChem)*
1:40 - 1:45 pm	Polyynes to polycycles: New approaches to the rapid assembly of π-rich materials. ***Ahmad El-Hawli*** *(MedChem)*
1:45 - 1:50 pm	Developing Small-molecule Activators of CaMKK2 as Potential Therapies for Bipolar Disorder. ***Abbey Muller*** *(MedChem)*
1:50 - 1:55 pm	Improving Neural Network Potentials for Quantum Chemistry. ***Teng Jiek See*** *(MedChem)*
1:55 - 2:00 pm	Acylsilanes as Acyl Anion Equivalents via Photochemically Generated Siloxycarbenes. ***Rowan Pilkington*** *(MedChem)*
Oral Presentation Session 3 *Chairs: Bilal and Ali*	LECTURE THEATRE 5
2:05 - 2:20 pm	Therapeutic potential of pro-resolving agonist in pulmonary arterial hypertension. ***Ting Fu*** *(DDB)*
2:20 - 2:35 pm	Dr PaCS-MD or how I learned to stop worrying and love in silico peptide affinity prediction. ***Viktor Prypoten*** *(MedChem)*
2:35 - 2:50 pm	Chemotherapy remodels sympathetic neural architecture to facilitate the growth of liver metastasis. ***Annabel Manoleras*** *(DDB)*
2:50 - 3.05 pm	Trans-tympanic delivery of antibiotics for the non-invasive topical treatment of acute otitis media. ***Hooi Leong Loo*** *(School of Pharmacy, Monash University Malaysia)*
3:05 - 3:20 pm	Preservation of Small Extracellular Vesicles in Dry Powder Form Using Spray Drying. ***Hong Hao Chan*** *(School of Pharmacy, Monash University Malaysia)*
02:30 - 03:00 pm	**Finalists Poster Presentation Round *(Concurrent)***
Afternoon Tea & Closing Ceremony	COSSAR HALL
3.45 - 4:00 pm	**Afternoon Tea**
4:00 - 5:00 pm	**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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	Tianxu Wang	MPharmSc
	Jeremy Salcedo	MPharmSc
Pharmacy intern Representative	Yannee Liu	Pharmacy Intern

PLENARY SPEAKER

Dr Kathy Nielsen

MPharm M IP Law PhD GAICD

Dr Kathy Nielsen is CEO of BioCurate, The University of Melbourne and Monash University's research translation joint venture focusing on therapeutics. Dr Kathy Nielsen brings over 25 years of experience in senior leadership roles primarily in the life science sector, with deep experience in technology transfer, venture capital, creating and advancing spin out companies, licensing and operating in the nexus between research and the pharmaceutical industry. Previously, Kathy was Senior Director of Commercialisation at Monash Innovation, responsible for a large team and portfolio of IP and commercial opportunities. During this period, she led Monash Innovation through a period of growth, building a robust pipeline, an expert transaction-oriented team and demonstrated success in global licensing and securing investment. Kathy was Senior Investment Manager at Queensland Investment Corporation, which managed four VC funds (in Au and USA).

Track Record

- Dealmaking: 100+ Licensing, Partnerships, Investment & Exits
- Spun out/invested in 42 life science companies
- New fund set up, investment management (5 funds) & IC member (6 funds)
- Drug development (discovery → late clinical) across therapeutic areas & modalities
- Held 22 board positions in biotech companies

JUDGES

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

JUDGES	THEME
Orals	
Dr Emily Pilkington	D4
Dr Aaron Day	MedChem
Dr Dorothy Wai	MedChem
Dr Laura Humphrys	DDB
Posters	
Dr Jon Merlin	DDB
Dr Andres Felipe Leon Rojas	MedChem
Dr George SQ Tan	CMUS
Dr Natalie Diepenhorst	DDB
Dr Rekha Shandre Mugan	D4
Dr Theo Nettleton	DDB
Dr Pouya Dehghankelishadi	D4
Dr Parisa Badiee	D4

AWARDS AND PRIZES

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

AWARDS	PRIZES	SPONSORS
Oral		
Most Outstanding Oral Presentation	$500.00	Sapphire Bioscience
Second Place Oral Presentation	$300.00	Eppendorf
Third Place Oral Presentation	$150.00	AAPS
People's Choice Oral Presentation Award	$150.00	BMG Labtech
Oral Presentation Encouragement Award	$100.00	KE Select
Poster		
Most Outstanding Poster Presentation	$300.00	Enimera RegsPlus
Second Place Poster Presentation	$200.00	Fisher Biotec
Third Place Poster Presentation	$150.00	BMG Labtech
People's Choice Poster Presentation Award	$150.00	Formulytica
Poster Presentation Encouragement Award	$100.00	Capella

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Formulytica is a specialist contract research, development, and manufacturing organization (CRDMO) delivering value to biotech and pharmaceutical companies wanting to outsource some or all of their early drug development programs. With our expertise in formulation development, analytical method development and validation, and small scale GMP manufacture for clinical trial supply, we offer a comprehensive set of R&D and manufacturing activities on-demand, to help our clients to seamlessly fast-track their path from discovery to launch, without the cost of hiring in-house R&D teams. Founded in 2015 by a team of PhD scientists with experience in the global pharmaceutical industry spanning many decades, we provide companies with comprehensive chemistry, manufacture and control (CMC) services to assist with the successful clinical development and registration of their new drug products. Formulytica can develop a wide range of formulations for prescription, over the counter (OTC) and cosmetic applications. Our main areas of expertise are topical drug delivery for dermatological applications, and also injectable drug delivery systems. We have successfully developed topical creams, gels, ointments, lotions, solutions, aerosol foams, injectable solutions and liposomal suspensions, and oral capsules and solutions. We have experience developing specialty drug delivery formulations including nanomedicines such as solid lipid nanoparticles (SLN). Formulytica is based in Melbourne, Australia, and has established a reputation as a world-class formulation and analytical development partner, for local biotech companies within Australia, as well as many clients from the US, EU, and Asia. With

our personalised approach, and our strong focus on innovation and quality, we deliver value to our clients, many of whom have entrusted us with multiple projects from their pipelines based on initial successes

American Association of Pharmaceutical Scientists (AAPS)

Founded in 1986, the American Association of Pharmaceutical Scientists (AAPS) is a professional, scientific organization of approximately 7,000 individual members and over 10,000 actively participating stakeholders employed in academia, industry, government, and other pharmaceutical science related research institutes worldwide.

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ABSTRACTS

Oral Presentation

Amir Hossain

Amir Hossain is a third-year PhD student at the Cancer Neural Immune Lab, Drug Discovery Biology. He completed his Master of Pharmacy (M.Pharm) from China Pharmaceutical University, China, and his Bachelor of Pharmacy (B.Pharm) from Manarat International University, Bangladesh. Currently, he is investigating the impact of the sympathetic nervous system on antitumor immunity in breast cancer under the supervision of Prof. Erica Sloan, Dr. Aeson Chang, and Prof. Scott Mueller.

MHC-II+ TAMs are present in responders of chemotherapy-beta-blocker combination therapy.

Preclinical and clinical studies are exploring the utility of pharmacological beta-blockade as a novel strategy to enhance existing cancer treatments. Beta-blockers block signalling from the sympathetic nervous system and have been shown to improve the efficacy of anthracycline chemotherapy in controlling metastasis in mouse cancer models and breast cancer patients. However, not all patients show a favourable response. To better understand factors that contribute to treatment response, we profiled the immune landscape of tumours in responder and non-responder mice. While the overall recruitment of F4/80+CD64+ macrophages, and CD4+ and CD8+ T cells to the tumour microenvironment were similar between responder and non-responder mice, mice that showed resistance to chemotherapy-beta-blocker combination treatment had lower levels of MHC-II+ tumour associated macrophages in the tumour, compared to responders. MHC II+ M1-like macrophages have been shown to have a tumour suppressive effect, suggesting the levels of MHC-II+ M1 tumour associated macrophages infiltration may influence the efficacy of chemotherapy and beta-blockade therapy. Ongoing experiments are examining a causal role for this cell types in the treatment enhancing effects of beta-blockers on chemotherapy.

Ali Esfandiary

Ali is focused on Parkinson's Disease diagnosis in his PhD research, identifying biomarkers through analytical method development using techniques like liquid chromatography-mass spectrometry (LC-MS) and matrix-assisted laser desorption/ionization (MALDI). His research is a collaboration between Prof. Nicolas Voelcker's & HMSTrust labs, The Florey Institute, and The Wicking Dementia Centre. Ali's expertise includes flow cytometry and designing both in-vitro and in-vivo experiments, along with experience in machine learning using R programming. When not working on his PhD, Ali enjoys exploring cognitive psychology literature and playing chess online.

Biomarker Discovery in Parkinson's Disease- a comprehensive look at sphingolipids pathway.

In our research, we explore the role of sphingolipid pathway alterations in Parkinson's disease (PD), focusing on the inconsistent findings regarding β-glucocerebrosidase (GCase) activity. We have observed that changes in the sphingolipid pathway, especially in ceramides and sphingomyelins, are systemic features present in idiopathic PD (iPD) serum. To address the inconsistencies in GCase activity data, we shifted our focus to the fate of accumulated GCase substrate (glucosylceramide; GlcCer) in cases of deficient GCase activity. Our hypothesis suggests that sphingolipid pathway flux changes may compensate for GCase deficiency by utilizing excess GlcCer to produce other sphingolipids, particularly gangliosides. This approach examines the impact of the GBA gene knock-in mutation on sphingolipid pathway flux, specifically focusing on ganglioside levels in mice brain tissues. By investigating potential compensatory mechanisms through ganglioside production in the brain, we aim to provide new insights into PD pathogenesis, explain inconsistencies in GCase activity data, and potentially uncover new biomarkers and therapeutic targets. This focused approach to studying sphingolipid alterations in the brain of GBA knock-in mice may offer a more comprehensive understanding of the underlying mechanisms in PD and the role of GBA mutations in the disease process. We provided new insights into PD pathogenesis by exploring the potential compensatory mechanisms in the sphingolipid pathway, which may help explain the complex relationship between GCase activity, lipid metabolism, and PD development.

Ting Fu

Ting is a final-year PhD student at the Cardiovascular Pharmacology Laboratory of the Monash Institute of Pharmaceutical Science. She is supervised by Dr. Chengxue Helena Qin, with co-supervision from Professor Rebecca Ritchie, Associate Professor Barbara Kemp-Harper, and Dr. Elva Zhao. Her doctoral research focuses on the regulation of formylpeptide receptors in cardiopulmonary diseases. She aims to understand the underlying mechanisms and identify novel therapeutic strategies to improve current treatments and outcomes for patients with cardiopulmonary diseases.

Therapeutic potential of pro-resolving agonist in pulmonary arterial hypertension.

Chronic low-grade inflammation is a key contributor to pulmonary arterial hypertension (PAH). The crucial aspect of a self-resolving inflammatory response is that it limits the production of pro-inflammatory mediators, followed by tissue healing, eventually returning to tissue homeostasis. The nonselective formylpeptide receptor (FPR) agonist, Compound17b (Cmpd17b) and BMS-986235 have shown pro-resolution effects in the pulmonary vasculature ex vivo, but the impact of FPR agonists on PAH is not known. To investigate the therapeutic effects of FPR agonist in a mouse model of PAH. 9-week-old male C57BL/6J mice were randomly allocated to either normoxia (21% O2) or hypoxia (10% O2 in N2) cohorts. The hypoxia cohort received subcutaneous injections of sugen 5416 weekly for 4 weeks and was exposed to hypoxia for 28 days. In this study, the sugen/hypoxia (SuHx) cohort was randomly divided into four groups: (i) treatment-vehicle, treatment with FPR agonists (ii) Cmpd17b (50 mg/kg/day) or (iii) BMS-986235 (3 mg/kg/day), or standard clinical treatment (iv) sildenafil (0.3 mg/kg/day). The normoxia cohort received the treatment vehicle. Mice were culled and organs were collected for analysis of gene expression by qPCR. SuHx mice displayed a significant elevation in wet lung weight and RV/(LV+S), significantly elevated right ventricular systolic pressure (RVSP), and upregulated expression of mIl-6. Compared to BMS-986235 and sildenafil, Cmpd17b not only lowered the RVSP in SuHx mice, but also downregulated mIl6, mTnf-α, and mCtgf (Table). Our study will facilitate the development of pro-resolution therapy as a novel approach to treating PAH.

Matthew Rowe

Matthew Rowe is a third year PhD student in the Integrated Neurogenic Mechanisms Lab. His research investigates how neural-goblet cell interactions are disrupted in gastrointestinal disease using fluorescence microscopy and complex image analysis approaches. Alongside his PhD, Matthew works as a research officer in the MIPS imaging facility, and as a teaching associate for undergraduate and graduate pharmaceutical science units at MIPS.

Investigating the Neural Control of Goblet Cells.

Goblet cells (GCs) line the gastrointestinal mucosa and are critical for the production and secretion of mucus. Mucus forms a physical barrier that protects the gut against pathogens. Dysfunction of the mucus layer leaves the gut susceptible to damage. Mucus secretion is stimulated by several neurotransmitters, most notably acetylcholine (ACh) released from the enteric nervous system. The mucosa is also innervated by neurons originating outside of the gut, including those of sensory and sympathetic origin. The extent to which different classes of neurotransmitters regulate GC maintenance and mucus homeostasis is poorly understood. In this study, we selectively ablated neuronal subtypes in the colon to investigate the effect of denervation on GCs and mucus thickness. We treated wild-type mice with resiniferatoxin (RTX) to ablate sensory nerves, or 6-hydroxydopamine (6-OHDA) to ablate sympathetic nerves. The colon tissue was immunolabelled to assess differences in GCs, mucus thickness, and innervation using comprehensive image analysis workflows that we developed. The mucus layer was significantly thicker following sympathetic denervation compared to vehicle-matched controls (40.2±9.7um vs 14.6±3.2um, p=0.03, n=6). In contrast, sensory denervation resulted in a thinner mucus layer compared to vehicle controls (10.2µm vs 45.6µm, n=2). GC numbers and tissue morphology were unaffected by 6-OHDA denervation (n=6) and RTX denervation (n=5). Our study suggests that sensory and sympathetic nerves contribute to GC and mucus homeostasis. Future studies will assess the effect of enteric denervation on GCs. Further characterization of neuronal subtype signaling on GC dysfunction is critical to understanding gastrointestinal complications in human neuropathic disease.

Viktor Prypoten

Viktor Prypoten is a 2nd year PhD student in Faculty of Medicinal Chemistry, supervised by David Chalmers and Ray Norton. His main area of research is computational modelling of proteins and peptides, their dynamics, and interactions. He has worked on predicting structures of toxin-ion channel complexes, dynamics of disulfide-rich peptides, and computational tools that predict peptide binding affinity.

Dr PaCS-MD or how I learned to stop worrying and love in silico peptide affinity prediction.

Peptide drugs represent an exciting direction in pharmaceutical space, with a $40 billion market share and a projected revenue growth of > 6% per annum. They have found breakthrough successes in a multitude of applications from HIV fusion inhibitors to the GLP-1 agonists like semaglutide. However, computational prediction of how well peptides bind to their targets remains a challenging and poorly-explored problem - making peptide lead optimisation particularly tricky. The large size and slow dynamics characteristic of peptides mean that typical computational approaches used to predict small molecule binding affinity struggle or fail entirely when used for peptides. We have developed a novel computational method called contact Parallel Cascade Selection Molecular Dynamics (cPaCS-MD), that can accurately predict binding affinity in the range relevant to lead optimisation. We validated cPaCS-MD on a diverse set of protein-peptide complexes and demonstrated superiority in both speed and accuracy over a conventional computational binding affinity prediction method. cPaCS-MD is useful in a variety of peptide drug discovery applications, including accurate predictions of peptide affinity and assessment of docked structures.

Minakshi Baruah

Minakshi is in the third year of her PhD candidature in the Drug Discovery Biology theme here at Monash. She is interested in unraveling GPCR mysteries using pharmacology and the most sophisticated imaging technique- Cryo Electron Microscopy. She is a part of the Centre for Cryo-electron Microscopy of Membrane Proteins (CCeMMP) node at Monash.

Revealing the Hidden Face of GPCRs- Mapping Inactive states.

G protein-coupled receptors (GPCRs) are dynamic membrane proteins that present challenges for structural determination. Since 2017, cryogenic electron microscopy (cryo-EM) has transformed GPCR structural biology by enabling high-resolution structures of agonist-bound active-state GPCRs without crystallization. However, solving apo and inhibitor-bound GPCR structures by cryo-EM remains difficult. Achieving these structures would unlock new drug discovery opportunities. Nb6, a nanobody that binds to the inactive κ-opioid receptor (κOR) ICL3, can be grafted into other class A GPCRs, allowing it to stabilize their inactive states. This strategy has enabled cryo-EM structures of the inhibitor-bound neurotensin 1 receptor, μ-opioid receptor (μOR), and the ligand-free somatostatin receptor 2. Nb6 also serves as a fiducial marker, aiding particle alignment for GPCRs with limited extra-membrane features. Here, we applied the Nb6 strategy to the vasopressin 2 receptor (V2R) to explore its interactions with non-peptide antagonists, including FDA-approved and clinically tested compounds. Using AlphaFold-based modeling, we designed nine V2R fusion constructs with varying lengths of κOR ICL3. These were characterized in a BRET assay to measure Nb6 binding in the absence of agonist and antagonist-mediated inhibition of this interaction. Constructs with high AlphaFold prediction confidence for rigid helical fusion points exhibited stronger BRET signals, indicating better Nb6 binding. One construct was prioritized for cryo-EM studies, but Nb6 dissociation during vitrification hindered high-resolution structure determination. While further biochemical optimization is needed, our pharmacological and structural studies demonstrate the potential of the Nb6 strategy for stabilizing inactive GPCR states for cryo-EM analysis.

Siobhonne Breen

Siobhonne Breen is a PhD candidate at the Monash Faculty of Pharmacy and Pharmaceutical Science, rationally optimising antibiotic combinations against resistant bacterial 'superbugs'. Siobhonne's project encompasses a range of laboratory work as well as mechanism-based mathematical modelling, both of which she has a strong interest in. Siobhonne has a passion for improving patient outcomes through drug research and development. Siobhonne has won multiple poster presentation awards and has been invited to given oral presentations at international and national conferences.

Ceftolozane/tazobactam plus meropenem against ST235-clone Pseudomonas aeruginosa isolates in HFIM.

Antibiotic resistance is one of the greatest threats to humans, an issue exacerbated by the Pseudomonas aeruginosa (Pa) high-risk ST235-clone, which is causing large concern for hospitals globally. Optimised dosing regimens are required to treat infections caused by this clone. To investigate ceftolozane/tazobactam (C/T) and meropenem (MER), in monotherapy and combination, against ST235-clone Pa isolates, in a dynamic in vitro hollow-fibre infection model (HFIM). Three multidrug-resistant ST235 isolates were investigated in 240h HFIM studies (n=1-2 replicates; inoculum ~106.8 CFU/mL). The pharmacokinetics of intermittent C/T (t1/2=2h) and continuous infusion MER (6g/day) in hospitalised patients were replicated in the HFIM and confirmed by LC-MS/MS. Quantified total viable and resistant bacterial counts were subjected to mechanism-based mathematically modelling (MBM) and whole genome sequencing was performed. Against all isolates MER monotherapy failed and amplified resistance by ~48h, while C/T monotherapy followed the same trend for two of the isolates. In one isolate C/T monotherapy reduced counts and suppressed resistance until 240h. The combination was synergistic (≥2 log10 CFU/mL killing compared to the initial inoculum and the best performing monotherapy) and suppressed resistance until 192h for all isolates. The model informed by the resistance mechanisms present well described antibacterial effects of the monotherapy and combination regimens. Discussion: The combination of C/T and MER enhanced bacterial killing, consistently suppressing regrowth and resistance against all ST235 clone Pa isolates tested. As this combination regimen demonstrated very promising activity, further investigation is warranted.

Darshna Goordeen

Darshna is a PhD candidate from the Centre for Medicine Use and Safety at Monash University. Her research aims to investigate deprescribing diabetes medication in older adults with a focus on those living with dementia, frailty, or receiving end of life care. Darshna previously graduated from The University of Auckland with a Bachelor of Pharmacy (Hons) and completed a Graduate Diploma in Clinical Pharmacy at The University of Tasmania. During her career, she has worked as both a community and hospital pharmacist.

Diabetes Medication Recommendations for Older Adults: A Systematic Review of the Western Pacific.

The Western Pacific Region (WPR) has the fastest ageing population and 38% of the world's diabetic population. It is unknown to what extent medication management recommendations are included for older adults in Type 2 Diabetes (T2D) Clinical Practice Guidelines (CPGs). To identify T2D CPGs within the WPR and investigate whether antihyperglycemic medication management recommendations are relevant to older adults, frailty, dementia, and those receiving end of life care. MEDLINE, Embase, Scopus, guideline-specific registries and grey literature searches were performed. Data were extracted on guideline characteristics and recommendations relevant to older adults, those living with dementia, frailty, co-morbidities associated with ageing or receiving end of life care. Quality appraisal was performed using the AGREE II (Appraisal of Guidelines, Research and Evaluation) tool. From the 37 countries and areas of the WPR, 14 CPGs were included from 10 countries. Included CPGs had between 1-15 relevant medication management recommendations. Twelve CPGs recommended less stringent and/or individualised glycaemic targets focused on reducing hypoglycaemia. Six CPGs included deprescribing recommendations about de-intensification/simplification of complex regimens in older adults, those with co-morbidities associated with ageing and receiving end of life care. Quality of CPGs varied, with scope and purpose rated the highest. None of the identified CPGs comprehensively addressed the T2D medication management needs for our populations of interest. Further research is needed to support CPG development in these areas while considering the diversity of the WPR, such as differences in population size, health infrastructure, medication access and socioeconomic status.

Annabel Manoleras

Annabel is a final year PhD candidate in Drug Discovery Biology. Annabel's PhD explores the role of the sympathetic nervous system on chemotherapy resistance in metastatic triple-negative breast cancer. Using high-powered imaging analysis tools, Annabel maps the spatial relationships between sympathetic nerves and metastatic lesions within metastatic target organs, and investigates how these relationships change following chemotherapy. Outside the lab, Annabel enjoys hanging out with her cat, Persephone, coffee and wine.

Chemotherapy remodels sympathetic neural architecture to facilitate the growth of liver metastasis.

Metastatic triple-negative breast cancer (mTNBC) is an aggressive disease, with treatment limited to untargeted therapies, including chemotherapy. We previously found that TNBC hijacks the sympathetic nervous system (SNS) to impair chemotherapy efficacy by increasing sympathetic neural density and signaling in primary tumours. However, the role of chemotherapy on SNS nerves at the metastatic site, and the impact on metastasis, remain unknown. mTNBC was studied using the MDA-MB-231HM orthotopic mouse model. Following primary tumour resection, mice with metastasis were treated with doxorubicin (vs. vehicle; i.v; 3% isoflurane/O2 anaesthesia; AEC #41818, 40522). Sympathetic innervation in liver was visualised using immunostaining for tyrosine hydroxylase (TH) and analysed for proximity to metastatic lesions. Doxorubicin treatment increased the diameter of TH+ varicosities in liver by 1.3-fold (veh vs. dox: 3.7µm±0.2µm vs. 4.8µm±0.3µm, p=0.02, n=8/group) and nerve density by 1.5-fold (0.11%±0.02% vs. 0.17%±0.02%, p=0.04, n=8/group). Following doxorubicin treatment, TH+ nerves branched further from the hepatic vasculature (increased average distance: 2-fold, $p < 0.0001$). Treatment with carboplatin chemotherapy similarly remodeled neural architecture and these findings were validated in a second model of mTNBC (4T1.2). Doxorubicin treatment led to spatial reorganisation of macro-metastases, moving their location further from TH+ nerves and associated hepatic vasculature (lesions >600µm from TH+ nerves:14% vs. 40%; n=8/group). These findings suggest that chemotherapy remodels the SNS at the sites of distant metastasis, possibly altering the spatial organisation of liver metastasis. Ongoing experiments aim to determine the impact of treatment on neural signaling and the effect of treatment-induced neural remodeling on disease progression.

Milad Ghorbani

Milad Ghorbani holds a Master's degree in Chemical Engineering- Biotechnology from the University of Tehran, Iran, and is now doing his PhD in Kempe group at Monash University, Faculties of Engineering and Pharmacy and Pharmaceutical Sciences. His research interests are in development and enhancement of inorganic/organic nanozyme systems using advanced polymer chemistry tools.

A Comparative Study on Surface-engineered Nanoceria: Colloidal Stability vs. Antioxidant Activity.

Nanoceria (NC) are widely studied as potent nanozyme antioxidants, featuring unique multifunctional, self-regenerative, and high-throughput enzymatic functions. However, bare NC are reported to show poor colloidal stability in biological media. Despite this, the nexus between colloidal stability and antioxidant activity has rarely been assessed. Here, a library of three copolymeric stabilising agents is synthesised, each consisting of hydrophilic poly(oligo(ethylene glycol) methyl ether methacrylate) brushes (P(OEGMA)) and a novel catechol anchoring block, and used for surface engineering of NC. The colloidal stability of the surface-engineered NC is assessed in phosphate buffered saline (PBS) by monitoring their precipitation via UV-Vis spectrophotometry, and their catalase (CAT)- and superoxide dismutase (SOD)-like activities are analysed using fluorospectrophotometry. The obtained results indicate that P(OEGMA) coating improves colloidal stability of NC over 48 h, highlighting the stable attachment of catechol functionalities to the surface of NC. In addition, X-ray photoelectron spectroscopy (XPS) indicates that the catechol functionalities lead to an increase in Ce3+/Ce4+ ratio and the concentration of oxygen vacancies, depending on the number of catechol units. Altogether, surface engineering of NC optimally results in an increase in CAT- and SOD-like activities by, respectively, 41% (= 57.7% H2O2 elimination) and 78% (= 78.0% $O_2^{\bullet-}$ elimination) relative to bare NC, signifying a positive correlation between colloidal stability and antioxidant activity of the NC nanozymes.

Paulo Simon

Paulo Simon obtained his MSc in Chemistry in 2022 at the University of Melbourne under the supervision of A/Prof. Wallace Wong. In 2023, Paulo was awarded a scholarship to pursue a PhD with Dr Amandeep Kaur, where his research is currently focused on the development of fluorescent tools to study amyloids implicated in neurodegenerative diseases. He is very passionate about student welfare at Parkville, and particularly enjoy his role as the Treasurer of Parkville Postgraduate Association 2024. Outside of the lab, Paulo enjoys playing tennis.

Chemical Nose for Discriminating Amyloids in Neurodegenerative Diseases.

Dementia is a significant global health challenge and the second leading cause of death in Australia, with Alzheimer's disease being the most prevalent form. Amyloids, misfolded protein aggregates, play a central role in these neurodegenerative diseases. Distinguishing between different amyloid types and isoforms is critical for early diagnosis and therapeutic development. However, due to the conserved cross-β sheet architecture shared by amyloids, accurate discrimination remains a challenge. This project aims to develop a diagnostic device capable of differentiating amyloids involved in neurodegenerative diseases. The device leverages cross-reactive fluorophores, which interact with various amyloids to produce unique fluorescence responses. These differential fluorescence patterns are analysed using multivariate statistical methods, enabling the discrimination of amyloid types and their isoforms. The device was created by immobilising fluorophores on a glass surface, and upon exposure to amyloids, distinct fluorescent signatures are generated.This project holds the potential to distinguish amyloids at different stages of disease progression, offering a valuable tool for early diagnosis and better understanding of neurodegenerative conditions.

Chantel Mastos

Chantel is a final year PhD student of the Spatial Organisation of Signalling lab in Drug Discovery Biology. Her research aims to determine the influence of signal location in determining downstream GPCR-mediated responses. To achieve this, she uses novel optogenetic methods which take advantage of the spatiotemporal precision of light. She hopes her PhD will shine a light on the importance of considering where signals occur, not just when and why.

Shining a light on intracellular GPCR signalling using optogenetics.

G protein-coupled receptors (GPCRs) are a family of >800 cell surface receptors that – in addition to signalling from the cell surface – can also signal from intracellular membranes. The differential localisation of GPCRs at the plasma membrane or intracellular membranes results in location-specific production of second messengers that can confer unique downstream responses. However, methods commonly used to investigate intracellular GPCR signalling (e.g., endocytic inhibition, organelle isolation) can perturb global cellular processes with potentially confounding consequences. We hypothesised that developing a synthetic optogenetic system would allow us to control intracellular GPCR signalling with greater spatiotemporal control over receptor activation than conventional pharmacological methods. Our approach utilised a rhodopsin β2-adrenoceptor (opto-β2AR) chimera that couples to canonical Gs-mediated signalling in response to light. We targeted the opto-β2AR to intracellular membranes using novel targeting sequences and used confocal microscopy to confirm subcellular GPCR localisation. Light activation of the receptor at each location differentially increased cAMP accumulation and ERK phosphorylation. qRT-PCR also revealed unique responses of each targeted receptor at the transcriptional level. Our results demonstrate that targeted optogenetic receptors provide a complementary approach to pharmacological methods to probe intracellular GPCR signalling. Our synthetic system can be applied to diverse biological contexts to better understand GPCR signal compartmentalisation and to explore whether dysregulated localisation of GPCRs is pathologically relevant.

Imesha Lakmini Hettige

Imesha completed a BSc (Honours in Chemistry) from the University of Sri Jayewardenepura, Sri Lanka, and a Graduateship in Chemistry from the Institute of Chemistry Ceylon, Sri Lanka. She has always been passionate about the field of drug discovery and decided to pursue a PhD in Medicinal Chemistry at MIPS in 2022 under the guidance of Prof. Martin Scanlon and A/Prof. Ben Capuano to acquire the necessary skills to become an effective medicinal chemist. Her current research is focused on developing new chemical tools for understanding the biology of fatty acid-binding protein 4 using fragment-based drug design approaches.

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

Fatty acid-binding proteins are a family of small, water-soluble proteins. They play a complex role in the body including the trafficking of lipids, drugs and hormones. Moreover, FABPs play a significant part in modulating signalling in cells and have been associated with diseases caused by aberrant lipid utilisation. FABP4 is expressed in various tissues, with high levels in adipocytes and macrophages. Studies using FABP4 knockout mice suggest potential benefits for treating inflammatory diseases including diabetes and atherosclerosis. Developing compounds that bind to FABP4 could be valuable for treating metabolic disorders. However, the molecular mechanisms in which FABP4 influences biological processes are not fully understood. Existing high-affinity ligands for FABP4 have limitations, such as high lipophilicity and poor water solubility, making them unsuitable for studying FABP4 activity in cells. This project aims to develop selective, high-affinity ligands with better physicochemical properties to aid the investigation of FABP4's role in disease. A fragment screening identified a novel biaryl N-phenylimidazole fragment as an FABP4 binder. To develop higher affinity fragments, this and its analogues were used in microscale parallel chemistry and off-rate screening by Surface Plasmon Resonance. The chemical libraries of these fragments are designed to explore diverse three-dimensional pharmacophores at specific positions on the fragment core. Biophysical tools, including SPR, Isothermal Titration Calorimetry, NMR, and X-ray crystallography, are used to characterize the analogues with the highest affinities for ongoing design.

Hong Hao Chan

Chan Hong Hao is a PhD candidate from the School of Pharmacy, Monash University Malaysia, specializing in the development and stability of small extracellular vesicles (sEVs) for therapeutic and drug delivery applications. His research focuses on optimizing sEV formulations through spray drying to enhance their stability and enable long-term storage at various storage temperatures. By developing formulations that preserve the structural integrity and biological functionality of sEVs, he aims to address challenges in their transport and handling. His work contributes to the advancement of sEV formulations and their potential applications in various biomedical fields.

Preservation of Small Extracellular Vesicles in Dry Powder Form Using Spray Drying.

Small extracellular vesicles (sEVs) are secreted by various types of cells, delimited by a lipid bilayer, and cannot replicate on their own. sEVs are emerging as therapeutics and drug delivery systems due to their content, natural carrier properties, and nanoscale size. Although sEVs are generally stored at -80°C, this temperature is not suitable for their handling, logistical management or preserving the stability of the sEVs due to variations in their composition and source. Therefore, developing a stable and easily transportable formulation is desirable. Spray drying is a promising approach to prepare sEVs in dry form for ambient temperature storage. In this study, the development of an optimum formulation and a spray-drying condition was established, and the stability of the spray-dried sEVs was compared with that of freshly isolated ones stored at -80°C. Trehalose and Tween 80 were the most effective excipients, preserving the protein content and particle size of the spray-dried sEVs compared to those without them. Over 12 months of storage, the physical properties of sEVs spray-dried powder, along with the protein content, particle size, and morphology of reconstituted spray-dried sEVs remained stable for up to 3 months at 30°C with 75% humidity and 6 months under cold conditions (-20°C and 4°C). In conclusion, spray drying with trehalose and Tween 80 is an alternative formulation and approach for preparing stable sEVs in a transportable dosage form.

Hooi Leong Loo

Hooi Leong is a graduate research student pursuing his Doctor of Philosophy (Ph.D.) at the School of Pharmacy, Monash University Malaysia. His research area encompasses the development of polymeric materials for drug delivery and pharmaceutical formulations. Currently, his Ph.D. research centers around the use of polymeric micelles to deliver antibiotics across the eardrum through the trans-tympanic route to treat middle ear infections. He is a passionate and self-driven research student that enjoys spending his time in the lab planning and running experiments. In his spare time, he enjoys reading, watching movies, playing boardgames, swimming, and going to the gym.

Trans-tympanic delivery of antibiotics for the non-invasive topical treatment of acute otitis media.

Acute otitis media (AOM) presents as an inflammation of the middle ear secondary to a microbial infection. Predominantly affecting paediatric patients, approximately 80% of children will experience at least one episode of AOM by the age of three years. Unfortunately, current therapy for AOM relies on systemic antibiotics due to the inability of antibiotics to cross the tympanic membrane. This study aims to deliver antibiotics across the tympanic membrane using lauric acid-g-chitosan (LA-g-CS) polymeric micelles for the topical management of AOM.Carbodiimide-mediated N-acylation of chitosan polymers was used to synthesize LA-g-CS polymers. A 32 Factorial Design was used to optimize the preparation of ofloxacin-loaded LA-g-CS polymeric micelles, and the optimized formulation was characterized. The in vitro cytotoxicity, in vitro drug release, and ex vivo tympanic membrane permeation of the optimized formulation was also determined.In vitro cytotoxicity testing using an MTT assay revealed at concentrations of 0.01mg/mL to 0.1mg/mL the micelles exhibit greater than 70% cell viability in human skin keratinocytes (HaCaT), human skin fibroblasts (Hs27), and neuroblastoma (SH-SY5Y) cells. Ofloxacin release from LA-g-CS polymeric micelles began to plateau around 8 hours, achieving approximately 75.35% drug release at 12 hours when tested in vitro. Cumulatively, 56.63µg of ofloxacin permeated across Sprague-Dawley rat tympanic membranes ex vivo when using ofloxacin-loaded LA-g-CS polymeric micelles compared to 36.89µg when using ofloxacin alone after 12 hours of incubation.Findings from this study support the potential of LA-g-CS polymeric micelles as a trans-tympanic delivery vehicle for antibiotics.

Poster Presentation

Nicole Warne

Nicole is a final year doctoral student working in the Kempe group of Monash University's Drug Delivery, Disposition, and Dynamics theme. Her thesis focuses on the synthesis, characterisation, and testing of semi-crystalline poly(cyclic imino ether)-based polymer nanorods for drug delivery applications. Through combining the synthetic versatility of poly(2-oxazoline)s and poly(2-oxazine)s with crystallisation-driven self-assembly techniques, she has investigated the effect of changing polymer corona chemistry and drug conjugation position from a variety of angles. Her most recent publication in Advanced Healthcare Materials details the formulation of novel mycophenolic acid-conjugated nanorods and assesses their bio-nano interactions and immunosuppressive effect in vitro.

Effect of Conjugation Site & Corona Chemistry on the Therapeutic Activity of Nanorod-Drug Conjugates.

Biocompatible rod-shaped nanoparticles of controlled length can be produced through the heat-induced "living" seeded crystallization-driven self-assembly (CDSA) of poly(2-isopropyl-2-oxazoline)-containing block copolymers. With a hydrophilic poly(2-methyl-2-oxazine) or poly(2-methyl-2-oxazoline) corona these nanorods have proven non-cytotoxic, non-hemolytic and ideal for use as a polymer-based drug delivery system. This study demonstrates a facile, one-pot method for the synthesis of mycophenolic acid (MPA)-conjugated block copolymer "unimers" for use in seeded CDSA. Through altering block order during sequential monomer addition cationic ring-opening polymerization, MPA is conjugated to either the chain end of the core-forming or corona-forming block. This allows bioactive polymer nanorods to be prepared with MPA positioned at either the periphery of the corona, or at the core-corona interface of the nanorod formed during seeded CDSA. In vitro, these nanorods arrest growth in human T and B lymphocytes, with reduced effect in "off-target" monocytes when compared with unconjugated MPA. Furthermore, conjugation of MPA to the core-corona interface of the nanorods leads to a slower release and reduced cytostatic effect. This study offers a robust investigation into the effect of steric hindrance and corona chemistry on the therapeutic potential of drug-conjugated CDSA nanorods and demonstrates the potential of poly(2-oxazoline)/poly(2-oxazine)-based CDSA nanomaterials as effective drug delivery platforms.

Douer Zhu

Douer Zhu completed her Bachelor of Pharmaceutical Sciences in 2021. She is currently a third year PhD candidate in Prof Nicolas Voelcker's lab. Her PhD project focuses on developing a microfluidic biosensor based on organ-on-a-chip technology to objectively detect and measure nociceptive responses related to chronic pain.

"Pain-on-a-Chip" Platform for Discrimination of Various Chronic Pain Types.

Chronic pain is a heterogeneous, multi-mechanistic condition that significantly impacts the daily lives of sufferers. It is typically caused by plasticity in the sensory nervous system, which transforms acute injury detected by nociceptors into a persistent, unpleasant sensation. However, pain perception is influenced by subjective psychological, environmental, and social factors, and there is a lack of precise, objective protocols for diagnosing and treating chronic pain. To address this gap, we have developed a microfluidic 'pain-on-a-chip' platform that integrates recent advancements in biocompatible microfluidic technology with on-chip differentiation of nociceptor-like sensory neurons. Following neuronal differentiation, we employed on-chip live-cell calcium imaging to validate the chip's functionality. Our results show that the system can successfully distinguish between biofluids collected from animal models of different chronic pain conditions. This platform offers a promising objective, rapid, cost-effective, and minimally invasive method for identifying subtypes of chronic pain.

Sheridan Rodda

Sheridan is a pharmacist with 20 years of experience in clinical pharmacy. Whilst working at Monash Health she has implemented innovative, pharmacist-led models of care for patients with inflammatory bowel disease and liver disease. Alongside clinical practice, she is completing her PhD in health economics with a focus on advancing the methods for incorporating equity into health technology assessment. Her work strives to help make healthcare decision making both efficient and equitable.

Education-Related Inequality in Quality-Adjusted Life Expectancy.

Education-related inequalities in health outcomes exist. To evaluate equity impacts of healthcare funding decisions, the distribution of health across equity subgroups is needed. Quality-adjusted life expectancy (QALE) reflects the length and quality of life. We aimed to provide QALE estimates by level of educational attainment for the Australian population aged 25–100 years. Health-related quality of life (HRQoL) measured as a mean health utility score, was estimated from Wave 22 (2022) of the Household, Income and Labour Dynamics in Australia survey. Education level was defined as low for those not completing year 12, intermediate for attaining year 12 or other non-tertiary qualifications, and high for tertiary qualifications and beyond. Education-specific mortality rates in 2019 were estimated from linked 2016 Census of Population and Housing and Death Registrations data. Health utility was incorporated into life table models to estimate life expectancy (LE) and QALE. HRQoL increased with increasing level of education. Males aged 25 with a tertiary education had greater LE compared to those with low levels of education (60.9 vs 54.9 years), and experienced 36% greater QALE (39.9 vs 29.4 years). For 25-year-old females, LE was greater in those with a high versus low level of education (63.1 vs 59.5 years) with a 25% difference in QALE (36.9 and 29.5 years respectively). Large disparities in the quality and length of life exist across levels of educational achievement. Tailored policies addressing education-related health inequity are needed. We provide baseline data for future equity-focused economic evaluations in Australia.

Dominika Fuhs

Dominika is a PhD candidate at the Monash Institute of Pharmaceutical Sciences. Her PhD research focuses on the development of novel mechanisms-based mathematical models that can describe and predict full time-courses of bacterial growth and resistance emergence to combat multidrug-resistant bacteria that can cause life-threatening infections. She's passionate about investigating ways to treat resistant bacterial "superbugs" by optimising dosing regimens of currently available antibiotics in the fight against antimicrobial resistance.

The effects of multiple resistance mechanisms on Pseudomonas aeruginosa response to meropenem.

Meropenem (MEM) is used against Pseudomonas aeruginosa (PA) infections, but resistance mechanisms reduce its effectiveness. Mechanism-based mathematical models (MBMs) address limitations of pharmacokinetic/pharmacodynamic indices, such as the time free antibiotic concentration exceeds the pathogen's minimum inhibitory concentration (fT>MIC). Characterise the effects of different baseline resistance mechanisms on bacterial killing and resistance emergence; develop a novel MBM. 10-day hollow-fibre infection model (HFIM) studies using seven isogenic PA strains with OprD porin channel loss, MexAB-OprM efflux pump over-expression, AmpC β-lactamase over-expression, and their combinations. The HFIM simulated MEM pharmacokinetics for critically-ill patients with normal renal function. All viable counts on drug-free, 3×MIC and 5×MIC MEM-containing agar across all strains, five clinically relevant regimens and control (n=90 profiles) were modelled simultaneously. fT>MIC could not explain the differences in bacterial response between strains. For example, regimens achieving ≥98% fT>1xMIC suppressed regrowth and resistance of one strain, while even 100% fT>5xMIC failed to achieve this against two other strains, despite all three of these having the same MIC. In contrast, the MBM well characterised all bacterial outcomes of all seven strains with the same model structure and without estimating strain-specific drug effect parameters. The presence of resistance mechanisms led to different bacterial outcomes, even for strains with the same MIC. The developed MBM is the first model to directly translate all major mechanisms of MEM resistance in PA and their complex interplay. This model represents a first necessary step towards personalised therapy adapted to the individual and the infecting pathogen.

Aisling McEvoy

Aisling McEvoy is a PhD Candidate with the Centre for Medicines Use and Safety. Her research focuses on deprescribing benzodiazepine receptor agonists in people living with dementia. She is excited to find non-pharmacological approaches to assist with sleep as a replacement for benzodiazepines and z-drugs. Before starting as a PhD student, Aisling completed her BPharm and MPharm with Monash University. She was awarded Best Poster Presentation at the Monash Intern Foundation Program Poster Night for her research in The Alfred Hospital's psychiatric service. Aisling continues to work as a clinical pharmacist at The Alfred Hospital while completing her PhD.

Deprescribing BZRAs in the elderly and people with cognitive impairment: a systematic review.

Benzodiazepine receptor agonists (BZRAs) (benzodiazepines and z-drugs) can improve sleep. However, their potential harms include falls, fractures and hospitalisations. Deprescribing BZRAs can be beneficial for older adults and people with cognitive impairment (CI) as they are at heightened risk of adverse events. This review investigated the effectiveness of patient-directed, non-pharmacological interventions to support deprescribing of BZRAs for insomnia in older adults and people with CI. Embase, CENTRAL, Scopus, and Ovid Medline were searched in January 2024 with no publication date restrictions. Screening, data extraction and risk of bias assessments were conducted independently by two authors. Outcomes of interest included proportion of participants who ceased BZRAs, and medication, sleep, and clinical outcomes. Seventeen studies were included, examining the effect of education and multi-component interventions to deprescribe BZRAs. Deprescribing success varied across studies, but all resulted in BZRA cessations. Between ~50-92% of participants ceased BZRAs at follow-up after receiving an educational intervention; compared to ~2-45% for those in the comparator groups. Only one study investigated BZRA deprescribing in people with CI and found comparable efficacy to participants without CI. Providing education about BZRA harms and deprescribing processes leads to reduced BZRA use. Overall reduction in BZRA use is dependent on contexts including setting and type of education provided. The included interventions may be equally effective in people with CI. Despite awareness that BZRAs can contribute to CI, limited studies have investigated patient-centred approaches to deprescribe BZRAs in this population.

Abisola Ave-Maria Siedoks

Abisola obtained her Bachelor of Pharmacy at the University of Lagos, Nigeria. Given her interest in the utility of medicinal plants in the management of sickle cell anaemia, Abisola went on to industry research at the Federal Institute of Industrial Research, Nigeria, identifying potential bioactive phytochemicals. Presently, Abisola is a 3rd year PhD student in the Norton group conducting research that focuses on the structure, function, and evolution of peptides and proteins of the ShKT superfamily and the development of novel peptide-based inhibitors of protein kinase Cε interactions for the treatment and management of Type 2 diabetes mellitus.

Novel Peptide-Based Inhibitors of Protein Kinase Cε for the Treatment of Type 2 Diabetes Mellitus.

Type 2 Diabetes Mellitus (T2DM) is a multifactorial metabolic disorder characterised by defective insulin secretion, insulin resistance and chronic inflammation. The involvement of the lipid-activated novel protein kinase C (PKCε) in the progression of T2DM, has been demonstrated through gene targeting techniques. Chronic activation of PKCε has been implicated as a driver in these processes; a consequence of its phosphorylation of key proteins involved in insulin secretion and activity. The spatial specificity of PKCε activity has been linked to interaction with RACK2, the Receptor for Activated C Kinase 2 (aka Copb2) involved in the retrograde Golgi-ER transport of proteins. Consequently, blockade of the PKCε-RACK2 interaction has been viewed as a strategy to modulate the deleterious effects of PKCε. Using a proximity-based chemiluminescent assay to monitor the binding of lipid-activated PKCε to RACK2, we have discovered inhibitory peptides derived from the PKCε sequence. In particular, a pentapeptide derived from the N-terminal C2-like domain of PKCε potently inhibits this interaction. By contrast, a previously described PKCε inhibitor peptide, εV1-2, also derived from this region, exhibited no significant inhibition of the PKCε-RACK2 interaction in this assay. The pentapeptide exhibited good cell penetrating ability, when compared to TAT in the Split Luciferase Endosomal Escape Quantification assay. These findings highlight the potential of PKCε modulation via trafficking motif mimicry and afford an opportunity for the rational design of a novel generation of peptides for T2DM prevention and/or treatment.

Lee Wen Hwei

Lee Wen Hwei is a PhD candidate at Monash University, researching the use of Zerumbone to mitigate skin aging. She employs bioinformatics tools to discover the mechanisms of skin aging and validate her findings with in vitro assays such as cell viability assay and western blot. Lee is developing a nanoformulation to enhance the stability and bioavailability of Zerumbone and will conduct a human trial to assess its safety and efficacy on aged skin. With a background in Pharmacy and Nutrition, she is passionate about integrating natural compounds with advanced technology to address skin-associated diseases, contributing significantly to the field.

The Mechanism of Zerumbone in Mitigating Cellular Ageing: Molecular Targets Identification.

Skin ageing serves as a visible reflection of ageing process, a universal issue affecting all populations worldwide. Our study uses network pharmacology and molecular docking to investigate the underlying pathways involved in skin ageing and how Zerumbone targets these biochemical processes to mitigate skin ageing. Zerumbone mitigates skin ageing by reducing oxidative stress and inflammation, regulating apoptosis, maintaining hormonal balance, and supporting adaptive mechanisms necessary for cell survival, growth, and differentiation. These processes occur through the interaction of Zerumbone with its gene targets, which are IL6, Caspase 3, SRC, PPARG, PARP1, AKT1 and PTGS2. These findings highlight the potential of Zerumbone as a therapeutic agent for mitigating skin ageing. Future research should investigate the potential applications of Zerumbone in clinical settings and its long-term effects on skin health.

Renad Albar

Renad is a third year PhD student, under the supervision of Ray Norton. Her project is focused on peptides derived from sea anemones as therapeutic and bioinsecticide candidates: structural and functional studies.

Structure and functional studies of Avt1, a novel peptide from the sea anemone Aulactinia veratra.

Sea anemones are a rich source of peptide toxins spanning a diverse range of biological activities, typically targeting membrane proteins such as ion channels, receptors and transporters. These peptide toxins and their analogues are usually highly stable and selective for their molecular targets, rendering them of interest as molecular tools, insecticides and therapeutics. Recent transcriptomic and proteomic analyses of the sea anemone Aulactinia veratra identified a novel 28-residue peptide, named Avt1. Avt1 was produced using solid-phase peptide synthesis, followed by oxidative folding and purification of the folded peptide using reversed-phase high-performance liquid chromatography. The liquid chromatography-mass spectrometry profile of synthetic Avt1 showed a pure peak with molecular mass 6 Da less than that of the reduced form of the peptide, indicating the successful formation of three disulfide bonds. The solution structure determined by NMR revealed that Avt1 adopts an inhibitor cystine knot (ICK) fold, in which a ring is formed by two disulfide bonds with a third disulfide penetrating the ring to create the pseudo-knot. This structure provides ICK peptides with high structural, thermal and proteolytic stability. Consistent with its ICK structure, Avt1 was resistant to proteolysis by trypsin, chymotrypsin and pepsin, although it was not a trypsin inhibitor. Avt1 at 100 nM showed no activity in patch–clamp electrophysiological assays against several mammalian voltage-gated ion channels, but has structural features similar to toxins targeting insect sodium ion channels. Although sequence homologues of Avt1 are found in a number of sea anemones, this is the first representative of this family to be characterised structurally and functionally.

Ahmad El-Hawli

Ahmad earned his Bachelor of Pharmaceutical Science with a major in Medicinal Chemistry here at MIPS. He began his research career during his honors under the guidance of Prof. Bernard Flynn, where he focused on developing methods for synthesizing scaffolds with multiple quaternary stereocenters. Currently, Ahmad is finalizing his PhD project, which is also centered on method development, specifically aimed at accessing π-rich materials.

Polyynes to polycycles: New approaches to the rapid assembly of π-rich materials.

Polyfused aromatic compounds (PACs) have unique electronic and optical properties due to their conjugated π-systems. They have been extensively researched over the past two decades and incorporated into a variety of applications including photonic material science, fluorescence imaging agents, and photoactivated drug therapies. These applications underscore the importance of these classes of compounds and their potential for innovative technologies and therapeutics. Currently, their development is limited due to the dearth of effective synthetic methods, limiting research efforts. In this work we describe the development of a novel approach to PACs through transmissive electrophilic poly-cyclisation (TEP). TEP exploits the ready synthetic accessibility of alkyne couplings in substrate construction and an electrophile-induced reaction cascade to enable ready access to well defined PAC structures. The products of these reactions are chiral and we are exploring methods for control of the diastereo- and enantioselectivity of their formation. Furthermore, we have shown that photochemically generated siloxycarbenes bearing an ortho-α,β-unsaturated ketone preferentially undergo an intramolecular 1,4-addition process to yield benzocyclobutenone silylenol ethers.

Abbey Muller

Abbey Muller completed her BSc in chemistry and pharmacology at Monash University's Clayton Campus before joining MIPS for her Honours in Pharmaceutical Science (Medicinal Chemistry). Her Honours research was focused on the synthesis of novel peptidomimetic AT2R agonists as potential anti-fibrotic agents. Abbey is currently undertaking her PhD under the supervision of Professor Bernard Flynn, Dr. John Scott and Associate Professor David Chalmers. Her research combines her interests in medical chemistry and drug discovery biology, focusing on validating the Calcium-Calmodulin Dependent Protein Kinase Kinase 2 (CaMKK2), as a potential therapeutic for bipolar disorder.

Developing Small-molecule Activators of CaMKK2 as Potential Therapies for Bipolar Disorder.

The Ca2+-calmodulin dependent protein kinase kinase-2 (CaMKK2) is a major transducer of Ca2+-signalling in cells, and a key regulator of brain function. CaMKK2 has emerged as a potential treatment target for bipolar disorder through converging evidence from genetic, mouse model, and biomarker studies. There is an urgent need for new medications to treat bipolar disorder as current therapies display limited efficacy and poor tolerability. We recently discovered that, in addition to Ca2+-calmodulin, CaMKK2 is also allosterically activated by long chain fatty acyl-coenzyme-A esters (LCFA-CoA). Our aim is to leverage this discovery to develop small-molecule CaMKK2 activators as chemical probes and potential therapies for bipolar disorder. Using purified CaMKK2 and a radiometric kinase assay, we screened LCFA-CoAs with different fatty acid chain lengths alongside a series of fatty acid-mimetic drugs, and also generated truncated and modified LCFA-CoAs, to identify the minimum requirements for CaMKK2 activation to reveal structure-activity relationships. We found that CaMKK2 activation is only activated by LCFA-CoAs with a fatty acid chain length between 14 and 16 carbons (i.e. myristoyl-CoA and palmitoyl-CoA). Palmitoyl-CoA was the most effective activator among the LCFA-CoAs tested, and activated CaMKK2 with a half-maximal concentration of 470 nM, which is within the physiological range and below its critical micelle concentration. Our findings have uncovered a novel allosteric mechanism that regulates CaMKK2 activity, which presents an exciting new strategy for the development of small-molecule CaMKK2 activators for use as chemical probes or potential therapeutics.

Foroogh Rezaei

Foroogh was raised in the historic city of Shiraz, south of Iran, and after completion of her Bachelor's Degrees in Applied Chemistry and English Language Translation, she moved to Isfahan University of Medical Sciences to do her Master's in Medicinal Chemistry. In addition to completing organic synthesis and pharmaceutical sciences subjects, she conducted a research project during her master's studies and it was published as a research paper entitled "Novel Catechol Derivatives of Arylimidamides as Antileishmanial Agents". She is currently undertaking her PhD, working on biosensors, under the supervision of Dr. Manuela Jörg and Prof. Nicolas Voelcker.

Novel Electrochemical Sensors for Rapid Identification of Carbapenem-Resistant Bacterial Infections.

Carbapenems are the most potent class of β-lactam antibiotics and the last line antibiotics for the treatment of multi-drug resistant Gram-negative bacterial infections. However, the emergence and rapid global dissemination of carbapenem resistance (CR) in recent years is of serious concern. The predominant mechanism of bacterial resistance to carbapenems is production of carbapenemases, the enzymes that cleave and inactivate carbapenem antibiotics. High mortality rates are associated with infections caused by carbapenemase-producing organisms, and the rapid spread of antibiotic-resistance has been largely attributed to human factors, such as misuse and overuse of antibiotics in general. The availability of rapid, easy-to-use, sensitive, selective, and low-cost diagnostic tools could promote appropriate prescribing practices, thereby slowing the spread of carbapenem resistance. Hence, we aim to develop an electrochemical biosensor for the rapid detection of carbapenem resistant bacteria strains. Electrochemical biosensors are highly sensitive and affordable and have low detection limits which can lead to their application for clinical samples ultimately. To this end, we have harnessed the predominant mechanism of CR, i.e., the bacterial production of carbapenemases, to target the detection of those secreted enzymes. Our probe consists of an enzymatic recognition motif like a carbapenem core linked to a redox moiety (inactive form). Upon bacterial enzymatic cleavage of the carbapenem core, the linker is released, and the redox moiety restores its electroactivity and an electrochemical signal is observed using voltametric methods such as cyclic voltammetry and differential pulse voltammetry.

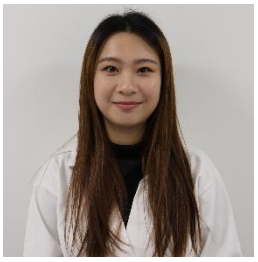
Chuhui Huang

Chuhui completed her Bachelor of Science (Honours) degree in Chemistry and Biological Chemistry (2009) and Master degree in Organic Chemistry (2012) at the Nanyang Technological University in Singapore. Under the supervision of Professor Philip Wai Hong Chan, her research project focused on gold- and silver-catalysed intramolecular amination and cycloisomerisation reactions to access N-heterocycles. She has previously worked at Baxter (Suzhou, China), Romer Labs (Singapore) and A*STAR (Singapore) before undertaking her PhD under Manuela Jörg's supervision at the Monash Institute of Pharmaceutical Sciences. Her research focuses on the development of chemical probes to assist target deconvolution in phenotypic drug discovery.

Targeted Protein Degradation: A Novel Target Deconvolution Method.

Phenotypic screening has resurged in recent years due to its capability to identify first-in-class therapeutics compared to target-based screening. However, elucidating the target protein of the hit compound remains a challenge due to the complexity of the process and the technology required to identify the target protein from a myriad of proteins within the biological system. Chemoproteomics is one methodology widely applied today in target deconvolution. Nonetheless, target deconvolution remains a challenging and time-consuming undertaking, and orthogonal methodologies are required to confirm the results attained from proteomics. Targeted protein degradation is a new method in drug discovery based on a novel mechanism of action. Targeted protein degraders are able to knock down or knockout target proteins in comparison to the conventional method of inhibiting protein targets. We envisage that targeted protein degradation has the potential as a novel methodology to elucidate the target proteins of hits identified from phenotypic screen programs. Here, we present the design, synthesis, and evaluation of novel chemical degrader probes targeting bromodomain-containing protein 4 (BRD4), which will assist with the development and validation of novel target deconvolution methods.

Lihuan Lin



Lihuan completed her Bachelor of Pharmaceutical Sciences degree (Honours) in 2021. She is currently in her third year of PhD under the supervision of A/Prof. Natalie Trevaskis and Prof. Ray Norton, focusing on the impact of lipidation on the pharmacokinetics, biodistribution and efficacy of peptide therapeutics in the treatment of autoimmune diseases.

Lipidation of HsTX1[R14A] alters its pharmacokinetics and biodistribution to target tissues.

Autoimmune diseases impact over 250 million people globally. Current therapeutics typically provide symptomatic relief or halt progression temporarily, but significant side effects and relapses are still major challenges for people with autoimmune diseases. Previous studies have shown that upregulation of the voltage-gated potassium channel Kv1.3 in effector memory T cells is associated with the pathogenesis of several autoimmune diseases. HsTX1[R14A] is a 34-residue (MW 3741 Da) disulfide-stabilised peptide that has picomolar potency and high selectivity for Kv1.3, and was effective in a rodent model of rheumatoid arthritis. However, like most peptides, HsTX1[R14A] is limited by rapid clearance, a short plasma half-life and non-targeted distribution, which necessitate more frequent dosing. Here we explored how lipid conjugation on HsTX1[R14A] affected its circulating half-life and its distribution in organs. We also investigated the distribution of the peptide to draining lymph nodes, as the pathological T cells that upregulate Kv1.3 are found predominantly in lymph nodes. HsTX1[R14A] was conjugated to lipids with various acyl chain lengths for pharmacokinetic studies, and Cy5 was conjugated to native and lipidated peptides for biodistribution studies. LCMS/MS assays were developed to quantify the lipidated peptides in mouse plasma. Conjugation of acyl chains to HsTX1[R14A] was found to extend its exposure in plasma and tissues after subcutaneous injection in mice at 2 mg/kg. Biodistribution studies using Cy5-labelled lipidated HsTX1[R14A] demonstrated enhanced exposure in disease-relevant organs and at the injection site at 4 h after subcutaneous injection (2 mg/kg). Cy5-labelled lipidated HsTX1[R14A] was also found to have increased accumulation in the liver compared to HsTX1[R14A] while having significantly less exposure in the kidneys at 4 h after subcutaneous administration. Thus, lipidation of HsTX1[R14A] is a promising approach to optimising its therapeutic potential by extending systemic exposure.

Boqun Liu

Boqun is a second year PhD student at MIPS major in Medicinal Chemistry. Her research interests focus on novel allosteric modulators and bitopic ligands towards aminergic GPCRs to address neurocognitive and neuropsychiratic disorders, in particularly, schizophrenia.

Discovery of Potent M1 and M4 mAChR Agonists for the Treatment of CNS Disorders.

The M1 and M4 muscarinic acetylcholine receptors (mAChRs) are promising drug targets for multiple CNS disorders including Schizophrenia and dementia. Guided by the structure M1/M4 dual agonist, compound 1, herein, we report the design, synthesis, pharmacological profile and structural investigation of a novel set of analogs. Structural modifications have been made to the (1) benzimidazole bottom, (2) bi-piperidine spacer and (3) the top methyl carbamate motif. Novel analogs were screened with both ERK functional and [3H] NMS radiolabel binding assays to quantify their Ach potentiating effect. Among them, compound 11a (hM4 EC50 = 1.91 nM, Ki =55.1 nM), and 13b (hM4 EC50 = 8.87 nM, Ki =33.4 nM) showed remarkable low nanomolar EC50 and was selected for molecular dynamic study. Taken together, compound 12a is worth further investigation as a tool compound to understand the interaction and binding preferences of mAChRs. The M1 and M4 muscarinic acetylcholine receptors (mAChRs) are promising drug targets for multiple CNS disorders including Schizophrenia and dementia. Guided by the structure M1/M4 dual agonist, compound 1, herein, we report the design, synthesis, pharmacological profile and structural investigation of a novel set of analogs. Structural modifications have been made to the (1) benzimidazole bottom, (2) bi-piperidine spacer and (3) the top methyl carbamate motif. Novel analogs were screened with both ERK functional and [3H] NMS radiolabel binding assays to quantify their Ach potentiating effect. Among them, compound 11a (hM4 EC50 = 1.91 nM, Ki =55.1 nM), and 13b (hM4 EC50 = 8.87 nM, Ki =33.4 nM) showed remarkable low nanomolar EC50 and was selected for molecular dynamic study. Taken together, compound 12a is worth further investigation as a tool compound to understand the interaction and binding preferences of mAChRs.

Ya Su

Ya Su is a final-year PhD candidate major in medicinal chemistry at Monash Institution of Pharmaceutical Science under the supervision of Prof Peter Scammells, A/prof Ben Capuano and A/prof Celine Valant. She has an interest in the development of small molecules targeting GPCRs for CNS disorders. Her project has focused on the development of hybrid ligands towards M4 muscarinic acetylcholine receptors for the treatment of schizophrenia and Alzheimer's disease.

The development and evaluation of novel hybrid ligands for M4 muscuranic acetylcholine receptors.

The M4 muscarinic acetylcholine receptor (mAChR) has been identified as promising target for many neurological disorders, including schizophrenia and Alzheimer's disease. Unfortunately, the clinical translation of drugs selectively targeting M4 mAChRs has proven difficult. For example, landmark studies with the M1/M4 mAChR preferring agonist, xanomeline, showed promising results in both a Phase III clinical trial for Alzheimer's disease and a proof-of-concept trial for patients with schizophrenia. However, a lack of mAChR subtype selectivity led to adverse side-effects mediated by off-target activity of xanomeline at peripheral M2 and M3 mAChRs. Encouragingly, M4 mAChRs can be targeted via allosteric modulators, able to recognize a distinct region on the protein, and subsequently alter the physiology of the receptor. Recently, 2-isoindol-3-(1H-pyrazol-4-yl)pyridine, XY6, a M4 positive allosteric modulator (PAM) attracted our attention as it exhibited noticeable allosteric activity in the presence of xanomeline while previous generation M4 PAMs failed. This discovery led us to hypothesise that rationally designed hybrid ligands based on xanomeline and XY6 could enhance the selectivity of xanomeline towards M4 mAChR while maintaining its favourable anti-psychotic and cognitive effects. In a major breakthrough, our laboratory has recently solved the cryo-EM structures of (i) xanomeline bound to the M4 mAChR, and (ii) XY6 co-bound with ACh at the M4 mACh. These findings can be incorporated in the design of novel hybrid ligands aiming for improved receptor selectivity towards M4 mACh. Herein, we report the design, synthesis and pharmacological evaluation of i) XY6 analogues with various attachment points on the pyridine core; ii) xanomeline analogues with various lengths of linkers; and finally, iii) xanomeline-XY6 hybrid ligands with polymethylene linkers.

Marisa G. Santibanez Moran

Marisa completed her BSc in Biological and Pharmaceutical Chemistry at the National Autonomous University of Mexico in 2020. During this time, she undertook a placement at MIPS where she worked with David Chalmers and David Manallack. Later, in 2021, Marisa completed her MSc in Drug Chemistry at Newcastle University, in the UK, where she received the prize for best overall student. Her MSc research project with Dr Kate Madden and Dr Agnieszka Bronowska focused on the design and synthesis of anti-inflammatory drugs. Currently, she is undertaking her PhD under the supervision of Manuela Jörg working on targeted protein degradation.

Development of fluorescent protein degraders for bromodomain-containing protein 4.

Targeted protein degradation is an emerging field that in recent years gained attention because it provides several advantages over traditional small molecule approaches. Despite numerous successful examples, PROTAC development still remains laborious and unpredictable. Understanding more about PROTACs mechanism of action in living settings would provide better guidance for their development. To address this, it is required to develop PROTACs with an extra functionality that allows to monitor protein degradation in cellulo. Previous studies have shown that it is possible to track the degradation of the protein of interest (POI) in vitro when a fluorescent ligand for the target protein is used as recruiting ligand in a PROTAC molecule. Here, we present the development of a trivalent PROTAC that comprises, together with the ligands for the POI and the E3 ligase, a fluorophore as a third functionality. This broadens the scope of fluorophores that can be used as it doesn't require to change the structure of any of the pharmacophores. We hypothesize that combining the visualization capabilities of fluorescent probes with PROTACs technology will enhance our knowledge about the mechanism of action and ternary complex formation in cells under different conditions. We designed and synthesised a set of trivalent fluorescent PROTACs (TFPs) targeting bromodomain-containing protein 4 (BRD4), a known cancer target. The TFPs were synthesised by connecting a fluorophore through varying linkers to the previously reported BRD4 trivalent PROTAC 1,2,5T-EG2-MZ1. This study proves that BRD4 trivalent PROTACs bearing a fluorophore as a third functional moiety can be developed.

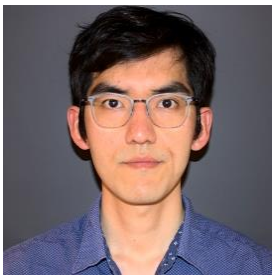
Teha Gebi

Mr. Teha Gebi is a PhD candidate in the Creek Lab, Drug Delivery, Disposition, and Dynamics at MIPS, Monash University. His PhD project aims to understand the metabolic cross-talk between malaria parasites and red blood cells. He holds a BSc in Medical Laboratory Sciences and an MSc in Medical Parasitology from the Institute of Health Science, Jimma University, Ethiopia. He has experience in both clinical settings and academia at Wolkite University in Ethiopia ah his previous research focuses on the epidemiology and control of infectious diseases, particularly malaria and soil-transmitted helminths.

Parasite-Host Metabolic Cross-Talk to Detect Malaria.

Current malaria diagnostic methods face practical and diagnostic limitations, often lacking the required sensitivity. Previous research in our laboratory revealed a fascinating phenomenon known as the bystander effect, where uninfected RBCs undergo glycolytic alterations when co-cultured with infected RBCs in the same culture dish. Given the relatively low number of infected RBCs in malaria patients, leveraging the bystander effect's influence on the more abundant uninfected RBCs could present a highly sensitive technique for malaria detection and offer insights into the disease's pathology. Bystander uninfected RBCs, when exposed to conditioned media from both asynchronous and synchronous cultures, exhibited a similar increase in phosphofructokinase activity. This suggests that the signaling factors derived from the parasite might not necessitate RBC rupture. We employed size-based fractionation, followed by exposure to bystander RBCs to the fractionated media and subsequent metabolomics analysis. The analysis revealed that the glycolytic alterations in bystander RBCs are driven by small molecules rather than proteins or extracellular vesicles. To assess metabolic perturbations in uninfected RBCs caused by malaria and their potential as diagnostic markers, clinical DBS samples were collected from healthy controls and malaria patients with a range of infection intensities in a malaria-endemic region of Ethiopia. Univariate and multivariate metabolomics analyses revealed metabolic signatures due to malaria including significant changes in glycolytic metabolites in both symptomatic and asymptomatic malaria cases compared to pyretic patients and healthy controls. The diagnostic accuracy of these metabolites was evaluated using ROC analysis. Pathway enrichment tests highlighted affected pathways beyond glycolysis.

Jun Yeob Kim



Kevin completed his Bachelor of Arts in Biology at Hunter College in the United States in 2015. He worked in the Bargonetti Lab for 5 years. His research during that period was based on MDM2-C, a splice variant of MDM2, by focusing on its biochemical aspects. In 2021, he completed MSc in Pharmaceutical Sciences in Trinity College Dublin, Ireland, with research focused on synthesizing levoglucosan-centered polymer through green chemistry. Currently, he is undertaking the PhD supervised by Dr. Manuela Jörg in Monash Institute of Pharmaceutical Sciences. His research is centered around the synthesis and evaluation of various dTAG molecules.

Development of Novel dTAGs to Study Role of Different Proteins.

The use of small molecules and genetic manipulation has failed to adequately understand the functions of certain protein populations. This has caused hindrance to drug discovery due to unforeseen protein behaviour, leading to adverse or nullified effects. dTAGs, which are heterobivalent molecules consisting of a FKBP12F36V-binding ligand, a linker, and an E3 ligase binder, are an alternative to conventional methods of protein function studies. They exploit cells' ubiquitination system and FKBP12F36V, an exogenous protein fused to a target protein for universal binding, to induce ubiquitin-mediated proteasomal degradation. While dTAGs have shown success in understanding proteins once deemed unapproachable, some targets still remain resistant due to a lack of available dTAG tools. Thus, the project aims to build a library of novel dTAGs with different E3 ligase binders. Our initial results include successful multi-gram scale synthesis of FKBP12F36V ligand and commercial dTAGs. The next steps include the synthesis and validation of novel dTAGs.

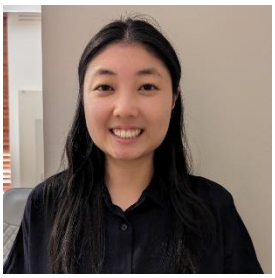
Ethan Kreutzer

Ethan is a third-year PhD student in the Drug Delivery, Disposition and Dynamics theme. He initially trained as a clinical pharmacist and is currently undertaking his graduate research studies in the Nicolazzo Lab focusing on drug transporters and Alzheimer's disease.

Disease-related factors affecting P-glycoprotein abundance in brain endothelial cells and microglia.

Alzheimer's disease (AD) results in pathological changes, including blood-brain barrier (BBB) alterations and microglial activation. P-glycoprotein (P-gp), a key BBB transporter, has been shown to be reduced in both abundance and function in AD, although the factors triggering this change remain unclear. Additionally, microglia express functional P-gp, potentially indicating a role for microglial transporters in contributing to drug distribution within the brain. Despite microglial phenotypic changes, less is known about mechanisms regulating microglial P-gp abundance, as has been studied at the BBB. Given that the apolipoprotein E (apoE) genotype is strongly linked to sporadic AD development and neuroinflammation is considered to be a key component of AD pathophysiology, our studies sought to assess the impact of these two AD-associated factors on P-gp abundance, both at the BBB and in microglia. Human cerebral microvascular endothelial cells (hCMEC/D3) were utilised as a BBB model and were exposed to recombinant human apoE3 or apoE4 at 2 µg/mL or 10 µg/mL, or to astrocyte-conditioned media (ACM) from astrocytes secreting humanised apoE for 72 hours. SR12813, a compound known to increase P-gp abundance, was utilised as a positive control (5 µM for 72 hours). To model inflammation, murine microglial cells (BV-2 cells) were exposed to 1 µg/mL of LPS for 24 hours to induce microglial activation. P-gp abundance was determined via western blot in both cell types. A quantitative absolute targeted proteomics (QTAP) approach was also implemented to assess changes to microglial transporter abundance. Treatment with SR12813 increased P-gp abundance in hCMEC/D3 cells approximately 1.5-fold, demonstrating that transporter abundance can be regulated within the cell system. However, P-gp abundance was unchanged after 72 hour treatments with recombinant apoE4 treatment relative to apoE3. Abundance of P-gp remained unchanged after exposure to apoE isoforms with ACM. QTAP indicated that treatment of BV-2 cells with 1 µg/mL LPS reduced P-gp abundance and a reduction by approximately 1.6-fold was confirmed via western blot. Although differences in apoE isoform have no direct influence on hCMEC/D3 P-gp abundance, LPS-mediated inflammation of BV-2 cells leads to a loss of microglial P-gp abundance. Our results indicate that microglial transporter mechanisms may be compromised in AD by inflammation, contributing to a loss of homeostatic function. Future studies are planned to determine potential mechanisms to restore microglial transporters through therapeutic intervention.

Annie (Mey Lee) Ea



Annie Ea is a PhD student at the Centre for Medicine Use and Safety and a clinical pharmacist at Alfred Health, primarily practicing in general medicine and geriatric medicine. Annie's PhD research investigates strategies for clinical practice guideline implementation in residential aged care, with a focus on healthcare professionals as knowledge brokers.

Strategies for generating and translating evidence for better medication management in aged care.

High quality evidence is integral to providing safe and effective medication management for residents of aged care homes. Residents are often under-represented in trials of medication safety and effectiveness. These gaps present a challenge to clinicians because evidence from clinical trials and observational studies on community-dwelling older adults cannot necessarily be extrapolated to residents. A non-systematic search of bibliometric databases including PubMed, Embase, and Google Scholar was conducted across the domains of aged care homes, medications, and evidence generation and translation. Key articles that addressed generating and translating evidence in aged care were included. Reference lists of relevant studies were reviewed to identify articles for inclusion. We identified a range of resident-, facility- and system-related barriers and facilitators. Strategies for generating evidence include building effective partnerships with aged care providers, utilising novel trial designs, leveraging existing data, and knowledge sharing through international platforms. Strategies for translating evidence include using quality indicators for audit and feedback, provision of education and training, engaging internal and external stakeholders and development of local action plans, and guideline implementation tools. There is an emerging interest in the role of knowledge brokers to facilitate knowledge translation. Developing and strengthening strategies for generating and translating evidence is imperative to bridge existing evidence gaps, guide opportunities to ensure sustainable uptake of evidence-based practice and improve resident outcomes. Integrating outcomes prioritised by residents into future research and resident involvement in evidence-synthesis can ensure medication management strategies developed are tailored to residents' needs.

Kathryn Fincham

Kathryn completed her Bachelor of Pharmaceutical Science at Monash University in 2020. Following this, she went on to complete her Honours year with the Norton Research Group at the Monash Institute of Pharmaceutical Sciences and moved on to start her PhD in Medicinal Chemistry in 2022. Her research focuses on developing novel anti-infective peptides.

Enhancing the Cytosolic Delivery of Bioactive Peptides.

Peptide drugs offer many key advantages over small molecule drugs, including improved affinity and the ability to bind to 'undruggable' targets. However, peptides also present unique challenges, including the fact that they cannot traverse cell membranes. One such class of impermeable peptides is DINNN-containing peptides, which are high-affinity inhibitors of the interaction between the SPSB1, 2, and 4 proteins and inducible nitric oxide synthase (iNOS). When delivered to the cytosol of M1 macrophages, DINNN peptides have strong potential as host-directed antibiotics through their ability to extend iNOS lifetime and thus increase NO output. In an attempt to improve the delivery of these inhibitors, conjugation to cell-penetrating peptides (CPPs) was explored. Through the use of a Split Luciferase Endosomal Escape Quantitation (SLEEQ) assay, the cytosolic delivery and endosomal escape of a DINNN peptide conjugated to the CPPs TAT, RW4, and CPP9 were measured. Cytosolic delivery of the cargo peptide was enhanced significantly by each of the CPPs, although endosomal escape remained low. Despite this promising result, the peptide conjugates failed to significantly enhance NO production in vitro, suggesting that an even greater improvement in delivery is required. In light of this, we are exploring alternative strategies to improve delivery, including β-peptide hydrogels and silica nanoparticles. The results of these studies will be presented.

Muhammad Bilal Hassan Mahboob

Muhammad Bilal Hassan Mahboob is a 3rd Year PhD student in the Drug delivery, disposition, and dynamics (D4) theme at Monash Institute of Pharmaceutical Sciences (MIPS). He got his degree in Pharmacy (Pharm-D) from Pakistan. He has worked in different roles as a registered Pharmacist in Pakistan. He also has 5 years of teaching experience at the university level and working as a teaching associate at Monash University. His PhD project aims to design and synthesize Cationic Lipidated Oligomers to help slow down the problem of Antimicrobial Resistance (AMR). His project also focuses on Metabolomics for the determination of the mechanism of action of these antimicrobial cationic polymers. He is one of the current Education and Careers officers in the Parkville Postgraduate Association. Apart from studies, he is interested in exploring nature.

Cholesterol-terminated cationic lipidated oligomers (CLOs) as a new class of antifungals.

Infections caused by fungal pathogens are a global health problem. This creates an urgent need for new antimicrobial strategies. This report details the synthesis of lipidated 2-vinyl-4,4-dimethyl-5-oxazolone (VDM) oligomers via an optimized Cu (0)-mediated reversible-deactivation radical polymerization (RDRP) approach. Cholesterol-Br was used as an initiator to synthesize a library of oligo-VDM (degree of polymerisation = 5, 10, 15, 20, 25, 30, 40 and 50) with an α-terminal cholesterol group. Subsequent ring-opening of the pendant oxazolone group with various functional amines [i.e., 2-(2-aminoethyl)-1,3-di-Boc-guanidine (BG), 1-(3-aminopropyl) imidazole (IMID), N-Boc-ethylenediamine (BEDA), or N, N-dimethylethylenediamine (DMEN)], and quaternization yielded an 14 functional cationic lipidated oligomer (CLOs) library, which comprised different cationic elements with the same terminal lipid cholesterol element. These CLOs exhibited greater activity against all tested fungal pathogens (*Candida albicans*, *Cryptococcus neoformans*, *Candida tropicalis, Candida glabrata, Cryptococcus deuterogattii,* and *Candida auris*), compared to the bacterial pathogens (*Escherichia coli, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa* or methicillin-resistant *Staphylococcus aureus* [MRSA]). Specifically, the DMEN and BEDA (after deprotection) series exhibited the superior antifungal activities of 4-16 times greater [determined by minimum inhibitory concentration (MIC) in μg/mL] than the clinically relevant antifungal Fluconazole. Two 'hit' CLOs (Chol-DMEN-25 and Chol-BEDA-10) were identified, which inhibited both [single sp. (*C. albicans, C. tropicalis, C. neoformans,* or *C. gattii*) and dual sp. (*C. albicans* and *C. tropicalis*)] biofilm formation, and were able to attenuate mature biofilms, with a >50% mature biofilm biomass reduction at 128 μg/mL. Co-delivery of fluconazole with two 'hit' CLOs demonstrated additive and synergistic effects on the aforementioned single-species and dual-species fungi biofilms, with a synergy score (SS) ranging from ~3-15 and most synergistic area score (MSAS) ~13-29 (by Bliss independence model). The mechanistic studies (PI assay and nucleic acid release assay) revealed that these CLOs disrupted the integrity of fungal cell membranes. These results demonstrate that cholesterol-terminated CLOs are potential antifungal candidates.

Talal Alrubaie

Talal Alrubaie holds a Master's degree in Pharmaceutical Sciences, with a focus on Drug Discovery and Development, from Chapman University in Irvine, USA, and a PharmD from Taif University in Saudi Arabia. He is currently in his second year as a PhD candidate in the Medicinal Chemistry Department at the Pharmacy College of Monash University, working under the supervision of Professor Philip Thompson. Alongside his research, Talal serves as a lecturer at Albaha University in Saudi Arabia, where he actively contributes to both teaching and academic development.

Efficient Polymyxin Depsipeptides Synthesis using Solid-Phase, modified Yamaguchi, and NCL.

This study presents an optimized protocol for the efficient synthesis of polymyxin-related depsipeptides exploiting native chemical ligation as a means of peptide cyclization. This approach relied on the integration of solid-phase synthesis and a modified Yamaguchi esterification to yield the key precursor. By addressing challenges in peptide assembly and ligation, we have developed a robust and reproducible synthesis pathway. This work not only advances the synthesis of polymyxin derivatives but also establishes a valuable framework for the production of similar depsipeptides. The detailed protocol provided serves as a practical guide for researchers exploring the synthesis of complex peptide structures, facilitating further advancements in antibiotic discovery.

Hannah Jane Ross

Hannah completed her Bachelor of Pharmaceutical Science Advanced at Monash University. After completing honours in medicinal chemistry, Hannah was awarded the Cyril Tonkin Scholarship. She has since commenced her PhD candidature, continuing in medicinal chemistry research with the Priebbenow Group. Her research currently looks at the development of new organometallic reagents for asymmetric nitrene transfer catalysis, with the aim of using these chemical methodologies to advance discoveries in catalysis, materials, and pharmaceutical chemistry.

Distal C(sp^3)-H Amidation via Ind*Rh(III) Catalysed Nitrene Transfer.

Well represented across feedstock chemicals, complex natural products, and pharmaceutical agents, the ubiquity of the C-H bond cannot be overstated. As such, the ability to target C-H bonds as reactive sites within a molecule presents a significant opportunity to elaborate on molecular scaffolds—particularly those that are already synthetically mature. Transition metal-catalyzed C-H amidation is an emerging strategy for the direct formation of amides and offers the ability to install functionality from otherwise inert C-H bonds. Direct C-N bond formation in this manner enables the derivatization of complex molecular frameworks—while avoiding the prior installation of reactive precursors, or complex de-novo synthesis. With methodologies for C(sp^2)-H amidation well established, the discovery of novel catalytic methods for functionalization at difficult C(sp^3)-H centers remains a challenge. Recognizing the importance of amide bond formation in pharmaceutical chemistry, we present the discovery of a new synthetic method for the amidation of β-C(sp^3)-H bonds via inner sphere nitrene transfer catalysis. The use of a (heptamethyl)indenyl-derived Rh(III) catalyst in combination with a 2-pyridone ligand and dioxazolone nitrene precursor was explored to harness the reactivity of this system for the accelerated amidation of otherwise unreactive alkyl substrates.

Monica Suehiro

Monica is a PhD student at the Structural DynOmics lab in Monash University. She completed her Bachelor of Biomedical Science with Honours at Monash University. During her honours, she utilised CRISPR-Cas9, intestinal organoids, and phosphoproteomics to understand the role of CDK8 and CDK19 in maintaining intestinal homeostasis. Monica is interested in utilising physiologically relevant experimental models and multi-omics approaches to understand mechanisms of disease pathogenesis. During her PhD, she hopes to map the interactome of her protein of interest and utilise structural studies to characterise key interactions at the amino acid residue level.

Investigating the role of TDP-43 in mitochondrial dysfunction and neurotoxicity.

Transactive response (TAR) DNA binding protein 43 (TDP-43) is a ubiquitously expressed DNA/RNA binding protein that regulates vital cellular processes such as mRNA stabilization and alternative splicing. Recent studies have demonstrated TDP-43 to be a key trigger in neurodegenerative diseases such as Amyotrophic Lateral Sclerosis (ALS) and Frontotemporal Lobar Degeneration (FTLD). Although their etiology is unknown, pathogenic hyperphosphorylated and ubiquitinated cytoplasmic TDP-43 aggregates is a critical hallmark of neurodegenerative diseases; observed in 97% of ALS and 50% of FTLD patients. TDP-43 is a predominantly nuclear protein that can also translocate to the cytoplasm. Over-accumulation in the cytoplasm has been shown to cause aberrant TDP-43 aggregation. Importantly, aberrant mitochondrial mislocalization also leads to mitochondrial dysfunction and exacerbates TDP-43's neurotoxic effects. We have begun to generate proteomics data that precisely tracks the spatial and temporal development of TDP-43 pathogenesis. To achieve this, we have differentiated 3 ALS and 3 control iPSCs into motor neurons and closely monitored TDP-43 pathology from 4 weeks post-differentiation. We are conducting direct analysis on isolated nuclei, cytoplasm, and mitochondria, significantly expanding the pool of proteins we can study using mass spectrometry-based proteomics. This comprehensive approach promises to greatly enrich the depth of insights gathered from our proteomic study, providing insight into the changes in mitochondrial import observed in ALS patients' motor neurons. Our initial findings will not only illuminate the composition of mitochondrial proteins but also reveal how these proteins interact within protein networks. This understanding is crucial for translating proteomic data into practical insights into ALS pathogenesis. Ultimately, our proteomic research aims to contribute essential knowledge about interaction networks and offer valuable insights into the mechanisms underlying ALS progression.

Evgenia Konstantinidou

Evgenia obtained a BSc in Chemistry from Aristotle University in Greece and an MSc in Drug Design and Synthesis from Vrije University in the Netherlands. She is passionate about organic chemistry and research, with a keen interest in drug discovery. Currently, she is pursuing a PhD under the supervision of Prof. Martin Scanlon and Dr. Brad Doak, focusing on structure-based drug design and fragment-based screening by different NMR techniques and SPR.

Development of selective small molecule chemical probes to investigate FABP5 function.

Fatty-acid binding proteins (FABPs) are involved in the transport and metabolism of hydrophobic molecules such as fatty acids, hormones, and drugs. Beyond their primary role as chaperones, FABPs are involved in complex signaling pathways. Epidermal FABP, also known as FABP5, has been associated with cancer and metabolic diseases characterized by aberrant lipid utilization. However, its precise mechanism of action remains unclear and requires further investigation. To this end, potent and selective FABP5 chemical probes are needed. Our approach combines insights from literature and fragment-based screening (FBS) to develop high-affinity, selective chemical probes for FABP5. A literature review revealed a promising yet underexplored thiophenylamide scaffold, which demonstrated high affinity and favorable physicochemical properties but lacked selectivity FABP5. Our efforts focused on modifying the thiophenylamide scaffold using structural information from molecular docking and X-ray crystallography to achieve selectivity over FABP4, the FABP most closely related to FABP5. Our second approach involved a fragment screening cascade, where ligand-detect and protein-detect NMR identified two elaborated fragment hits. To explore the chemical space around the sulfonamide scaffold in an unbiased way, we performed off-rate screening (ORS) using SPR. A variety of diverse reagent sets covering common medicinal chemistry reactions were employed for high-throughput parallel small-scale synthesis. These minimally purified reaction mixtures were screened in parallel against FABP4 and FABP5 to identify unique FABP5 hits, which are then synthesized in batch scale and validated. We aim to conduct iterative parallel ORS rounds to explore different vectors along the scaffold, ultimately developing high-affinity and selective chemical probes for FABP5.

Rowan Pilkington

Rowan is a 2nd year PhD student within the Medicinal Chemistry theme at MIPS. After completing a Masters degree in chemistry at the University of Melbourne, Rowan worked at CSIRO, followed by Defence Material Technology (DMTC) developing process chemistry routes to API's using flow chemistry methods. In the Priebbenow Group, Rowan's research focuses on the utilisation of visible light to drive new reactions for synthetic chemistry.

Acylsilanes as Acyl Anion Equivalents via Photochemically Generated Siloxycarbenes.

Acylsilanes, a unique class of carbonyl compounds bearing a carbon-silicon bond, are known to undergo photochemical conversion to siloxycarbenes via 1,2-Brook rearrangement. Owing to inductive stabilisation of the siloxycarbene by the adjacent oxygen atom, the siloxycarbene is dominated by singlet, soft nucleophilic character. As part of our ongoing efforts to map the reactivity of acylsilane-derived siloxycarbenes, we have discovered highly efficient and selective “photo-click” reactions of siloxycarbenes and activated carbonyl compounds. Trifluoromethylketones and 1,2-dicarbonyl compounds can be engaged as reactive partners in an intermolecular 1,2-addition process requiring no exogenous reagents or catalysts other than visible light. Furthermore, we have shown that photochemically generated siloxycarbenes bearing an ortho-α,β-unsaturated ketone preferentially undergo an intramolecular 1,4-addition process to yield benzocyclobutenone silylenol ethers.

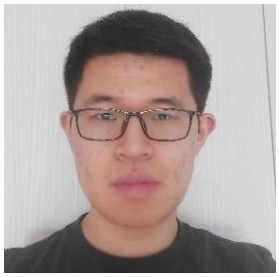
James Bowers

James Bowers completed a BPharmSci (Hons) at MIPS under the supervision of Prof. Jonothan Baell where he investigated formyl receptor antagonists. After graduating with first-class honours, he worked as a research assistant at MMIC before embarking on a PhD. Supervised by Dr. Daniel Priebbenow, his research explores hydantoins, with a dual focus on their utility in organic synthesis and as drug candidates for ryanodine receptor-linked heart failure.

Further uses of hydantoins as directing groups: Palladium-catalyzed C-H amination

Hydantoins (imidazolidine-2,4-dione), are a class of heterocyclic compounds, that are frequently seen as intermediates in biological processes. They have found applications in pharmaceuticals and agrochemicals. Due to their indisputable biological relevance, and use within our group's medicinal chemistry programs, large efforts have been made towards utilizing the hydantoin scaffold as a directing group in ortho-directed functionalization. We are reporting a palladium-catalyzed ortho-carbamation that uses hydantoins as directing groups and N-sulfonyloxy carbamates as nitrene sources. The reaction has been further enhanced with microwave irradiation. The Troc-protecting group can be readily cleaved to reveal the free amine.

Teng Jiek See



Teng Jiek See is a PhD student in Pharmacy and Pharmaceutical Sciences, specializing in Medicinal Chemistry, at Monash University (Parkville campus). His research focuses on developing AI models for molecular property prediction. Teng has published a paper in the Journal of Chemical Theory and Computation (JCTC) and holds a First-Class Honours degree in Pharmaceutical Science Advanced (Honours) from Monash. He is supervised by A.Prof David Chalmers, Dr Mario Boley, and A.Prof Daokun Zhang. In his spare time, Teng enjoys creating YouTube videos that simplify AI research for wider audiences.

Improving Neural Network Potentials for Quantum Chemistry

Quantum mechanics (QM) is computationally costly due to complex mathematical algorithms. Neural Network Potentials (NNPs) (such as ANI, DimeNet++) are used to approximate QM by training a neural network on QM datasets to produce accurate molecular property prediction. Current NNPs fail to reproduce QM prediction accurately due to poor chemical/physical representation architectures. In this work, we explore ways to improve the molecular property prediction by injecting chemical/physical inductive biases.

Alice Terrill

Alice is a second-year PhD candidate focusing on the optimisation of dosing regimens of antibiotics to overcome the antimicrobial resistance crisis. She has been the Student Representative of both the Population Approach Group of Australia and New Zealand (PAGANZ) and the Australian Society of Clinical and Experimental Pharmacologists and Toxicologists (ASCEPT) Drug Disposition and Response Special Interest Group. Through these she has supported with organising the PAGANZ 2024 Meeting, and developed the first ASCEPT-PAGANZ Joint Student Symposium. Alice enjoys sharing her research and has done so through Science Meets Parliament, on Triple RRR radio, Dose of Pharma Podcast and at Melbourne's Soapbox Science event.

Mathematical model predicts antibiotic effect on Pseudomonas aeruginosa where PK/PD indices cannot.

PK/PD indices are based on minimum inhibitory concentrations (MICs) and link bacterial response to antibiotic exposure. The index for ciprofloxacin (CIP) is the ratio of free drug area under the concentration-time curve to MIC over 24h (fAUC/MIC) and for meropenem (MER) it is the percentage of time the free concentration remains above the MIC (or a multiple of MIC) over 24h (%fT>MIC). The study evaluated if the effect of CIP and MER alone and in combination on isogenic strains of P. aeruginosa could be predicted by PK/PD indices or depended on resistance mechanisms present. Seven isogenic P. aeruginosa strains: PAO1 (wild-type reference strain), PAΔAD (ampD knockout/ampC overexpression), PAOD1 (oprD mutation/loss of porin OprD), PAΔmexR (mexR knockout/MexAB-OprM upregulation), PAΔADΔmexR, PAOD1ΔmexR and PAOD1ΔAD (combinations of these resistance mechanisms) were used. Strains were exposed to MER and CIP alone and in combination, over 72h. Mechanism-based mathematical modelling (MBM) was performed. PK/PD indices did not predict bacterial response. 1-4x MIC and fAUC/MIC of 48-384 for MER and CIP, respectively, were required to suppress regrowth across strains. PK/PD indices also do not predict combination therapies. An MBM was developed that described bacterial response to antibiotic based on resistance mechanisms, predicting mono- and combination therapies of MER and CIP. 292 treatments were modelled. PK/PD indices alone did not predict the MER or CIP exposure required to suppress bacterial regrowth, indicating mechanisms of resistance should be considered when optimizing dosing. An MBM, accounting for resistance mechanisms, could predict the impact of double mutations and combination therapies.

Qinghao Ou

Qinghao Ou is a CCeMMP PhD student in the Metabolic Receptor Biology led by Prof. Denise Wootten and Patrick Sexton. Qinghao's study focuses on the structural and mechanistic understanding of co-agonism in GLP-1R and GIPR by using conventional single-particle Cryo-EM with pharmacological assays.

Structural understanding of tirzepatide on GIPR and GLP-1R.

As of 2017, around 34% of the drugs approved by the US Food and Drug Administration (FDA) target G-protein coupled receptors (GPCRs). Understanding the structural details of ligand and transducer interactions with GPCRs and the relationship between GPCR structures, GPCR activation, signaling, and physiological functions are crucial to understanding how they function at the molecular level. The glucagon-like peptide-1 receptor (GLP-1R) and glucose-dependent insulinotropic polypeptide receptor (GIPR) are class B1 GPCR that bind incretin hormones and are involved in the control of post-prandial insulin secretion and glycemic homeostasis. These receptors are validated therapeutic targets for drugs to treat type 2 diabetes (T2D) and obesity. The surpassing success of tirzepatide (Mounjaro ™) compared to the GLP-1R-selective semaglutide in the type 2 diabetes treatment highlights the benefits of GLP-1R/GIPR co-agonism. But the more efforts were required to understand the molecular mechanisms of tirzepatide on GLP-1R and GIPR. Though there are existing published cryogenic electron microscopy (Cryo-EM) structures of tirzepatide-bound GLP-1R and GIPR, additional stabilization strategies were introduced during the sample preparation, including the NanoBiT tethering coupled with a mutation on GIPR1, and small-molecular positive allosteric modulators with agonism together with scFv162, respectively. These stabilization strategies may convolute the observed peptide: receptor interactions. In the current study, without applying any extra stabilization strategies mentioned above, we resolved Cryo-EM structures of tirzepatide-bound GLP-1R: dominant negative Gs (DNGs) at 3.0-3.2 Å (3 subclasses) and GIPR: DNGs and 2.4 Å, respectively. This allowed us to analyze the tirzepatide: receptor interactions on both receptors.

Nathan Bell

After a bachelor's degree in chemistry and pharmacology at the University of Otago, New Zealand, Nathan undertook an MSc in physical organic chemistry where his research examined the release mechanism of carbon monoxide prodrugs with Prof. David Larsen. After graduating with Distinction, he continued as a research assistant for Prof. Larsen, and then Dr Nick Green, where he worked on methodology projects to synthesise α-galactosides and pseudonucleosides. In 2023, he started a PhD with Dr Daniel Priebbenow, exploring the synthesis and applications of sp^3-rich isosteres of aromatic rings.

Strain-release synthesis of 2-azabicyclo[2.1.1]hexan-3-ones from bicyclo[1.1.0]butanes.

Nearly every drug molecule in use today contains an aromatic ring system. Despite their ubiquity, it has been shown that excessive use of aromatic rings can impart high lipophilicity, reduced solubility, and metabolic liability, which hinders progression through the drug development pathway. To mitigate these issues, bioisosteric replacement of aromatic rings with rigid, bicyclic, sp^3-rich scaffolds has been employed to improve physicochemical and pharmacokinetic properties. However, robust synthetic strategies to access such moieties are still in relative infancy. In particular, methodologies to synthesize isosteres of nitrogen-containing heteroaromatic motifs are extremely limited. In this presentation we report the synthesis of a unique 2-aza-bicyclo[1.1.2]hexan-3-one architecture via a strain-release [2π + 2σ] cycloaddition between bicyclo[1.1.0]butanes and isocyanates. The scope of the transformation and the three-dimensional structure are highlighted as a scaffold for drug design.

Kuan Wai Chee

Wai Chee is currently leading a health economics and outcomes research project on heart failure, with collaborators from 4 key cardiac centres in Malaysia (IJN, UMMC, UiTM, Hospital Serdang), Malaysian Health Technology Assessment Section, Universiti Sains Malaysia, King's College London and Monash University Australia (Health Economics and Policy Evaluation Research).

Trajectory of health-related quality of life of heart failure patients.

This study aimed to examine the trajectory in health-related quality of life (HRQoL) during and after hospitalisation for worsening of heart failure (HF) in Malaysia. 200 patients with heart failure and reduced ejection fraction (HFrEF) admitted into two hospitals in Malaysia due to worsening of HF were surveyed using the EQ-5D-5L questionnaire. The primary outcomes were utility values at admission, discharge and 1-month post-discharge (1MPD). Secondary outcomes include the visual analogue scores (VAS) and the proportion of patients reporting each EQ-5D-5L dimension levels. Missing data were imputed using multiple imputation, and generalised linear mixed models were fitted. At admission, the unadjusted mean utility values and VAS scores for HFrEF patients in Malaysia were as low as 0.150 ± 0.392 and 38.2 ± 20.8, respectively. After a median hospital stay of 4 days, there was a significant improvement in utility values and VAS scores by 0.510 (95% CI: 0.455 - 0.564) and 28.8 (95% CI: 25.5 - 32.1), respectively. The utility value and VAS score at 1-month post-discharge were not significantly different from discharge. The proportion of HFrEF patients reporting problems and severe problems in mobility, self-care, usual activities, and anxiety/depression, pain/discomfort reduced at varying degree from admission to discharge and 1MPD. Conclusion: HF is a progressive condition with substantial variation in HRQoL during the disease trajectory. During hospitalisation due to worsening of HF, HFrEF population has unfavourable HRQoL. Rapid and significant HRQoL improvement was observed at discharge, which sustained over one month. The study findings can inform future cost-effectiveness analyses and policies.

Chang Chee Tao

Mr. Chang, a Research Pharmacist at the Clinical Research Centre and a Doctorate in Pharmacy candidate at Monash University Malaysia, specializes in geriatric care. With over fifty peer-reviewed articles, he focuses on bridging academia and clinical practice to improve medication safety for the aging population. He leads initiatives like the World Health Organization's Age-Friendly program and co-developed the MALPIP deprescribing tool for Malaysian patients. Mr Chang's work primarily revolves around deprescribing studies, aiming to optimize medication regimens for older adults, thus enhancing their quality of life and well-being, showcasing his commitment to impactful healthcare.

Development of a Malaysian screening tool for potentially inappropriate prescribing in older adults (MALPIP): a Delphi study.

Polypharmacy and the use of potentially inappropriate medications (PIM) are prevalent among older adults. Healthcare professionals often use explicit criteria to guide appropriate prescribing, aiming to deprescribe inappropriate medications or initiate necessary treatments due to prescribing omissions. However, many of the existing PIM criteria lack robust guidance from quality metrics or the incorporation of real-world data.The aim of the study is to develop a list of medications to promote appropriate prescribing in older adults.A preliminary list of PIMs and potential prescribing omissions (PPOs) was compiled from a systematic review, supplemented with local pharmacovigilance data on adverse reactions in older adults. Twenty-one experts from nine specialties took part in two Delphi rounds to finalize the list of PIMs and PPOs. Items that failed to reach consensus after the second round were reviewed by six geriatricians for adjudication.The initial list included 406 potential candidates, divided into three sections: PIMs independent of disease, disease-specific PIMs, and omitted medications that could be restarted. Following the Delphi process, 92 items were finalized as PIMs, covering medication classes such as antacids, laxatives, antithrombotics, antihypertensives, hormones, analgesics, antipsychotics, antidepressants, and antihistamines. Additionally, 42 disease-specific PIM criteria were included, addressing conditions related to the circulatory, nervous, gastrointestinal, genitourinary, and respiratory systems. Consensus on starting omitted treatments was reached in 35 statements across nine therapeutic areas.This Malaysian PIM criteria list offers a practical tool for clinicians and pharmacists to identify PIMs and PPOs during medication reviews, supporting informed decision-making for optimal prescribing in older adults.

MONASH University

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